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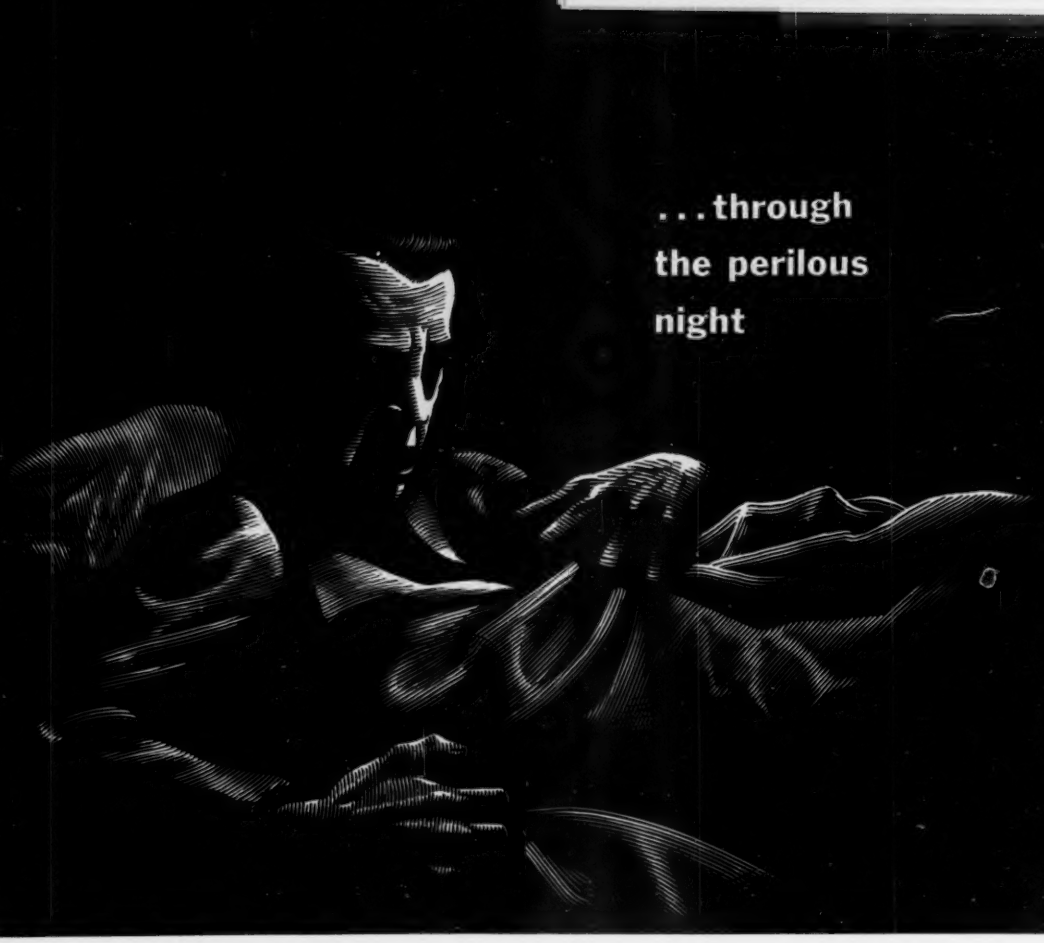

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1. Winsor, T., and Humphreys, P.: Angiology *3*:1 (Feb.) 1952. 2. Plotz, M.: New York State J. Med. *52*:2012 (Aug. 15) 1952. 3. Dailheu-Geoffroy, P.: L'Ouest-Médical, vol. 3 (July) 1950.

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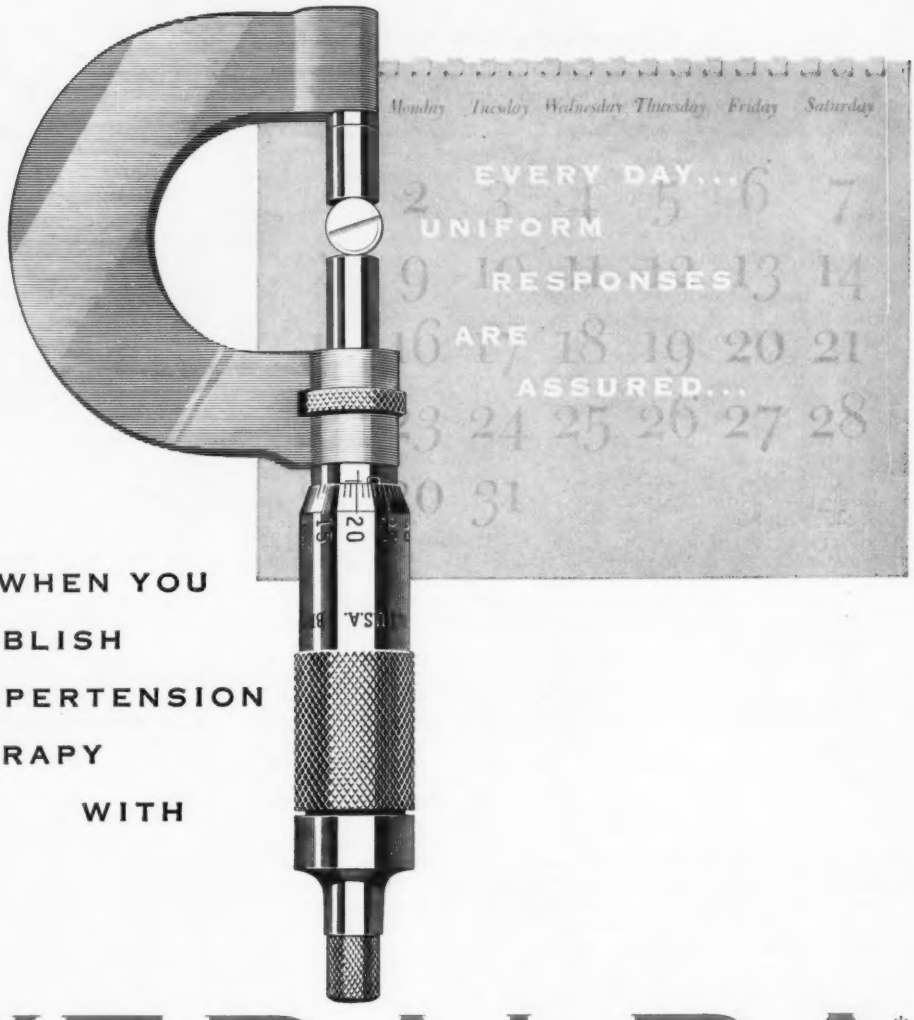

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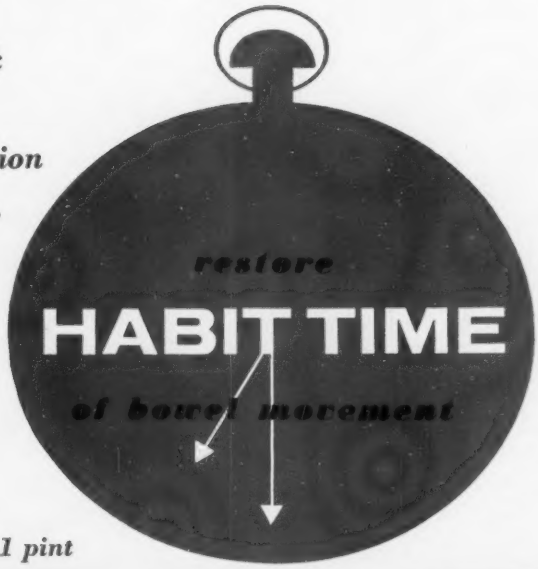

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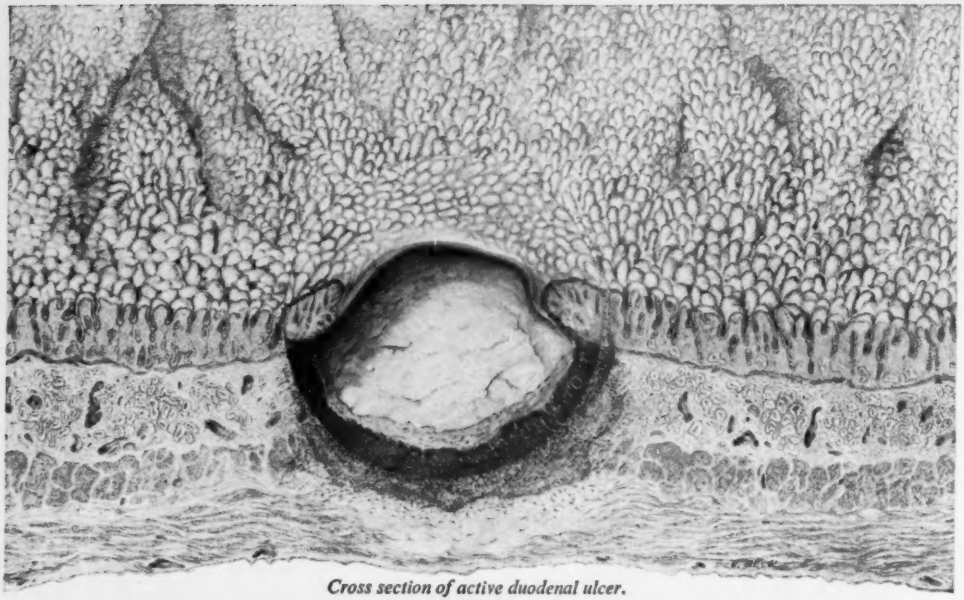

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2. Schwartz, I. R.; Lehman, E.; Ostrove, R., and Seibel, J. M.: A Clinical Evaluation of a New Anticholinergic Drug, Pro-Banthine, Gastroenterology *25*:416 (Nov.) 1953.

SEARLE

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Clinical States Associated with Alterations of the Hemoglobin Molecule

The Minot Lecture

HARVEY A. ITANO, M.D., Ph.D., Bethesda, Md.

The role played by Dr. William B. Castle, the first Minot lecturer, in stimulating the initial studies of hemoglobin in sickle-cell anemia is not generally known. It was his description, in 1945, of the effect of oxygen and carbon dioxide on sickling, in Dr. Linus Pauling's presence, which prompted Dr. Pauling to postulate that an abnormal hemoglobin was present in the sickling cells.[1] The following year, Dr. Pauling suggested that I begin the investigation which culminated in the detection of an inherited abnormal hemoglobin in sickle-cell anemia and sickle-cell trait.[2] By 1951 two more abnormal hemoglobins (Figs. 1-5) were found to be associated with sickle-cell disease.* By 1953, ten distinct hereditary clinical states were known to be associated with abnormal hemoglobin metabolism.[5] During the past year five more abnormal hemoglobins have been found,† two in clinical states resembling Cooley's anemia ‡ and two in asymptomatic states.§ While part of what I shall review comprises work done by my colleagues and me, much is due to the many other investigators now engaged in the study of abnormal hemoglobins. Surveys published in recent months have provided detailed lists of references to specific investigations.‖ Those interested are referred to the surveys, as no attempt will be made in this brief presentation to duplicate their completeness.

Sickle-cell disease and thalassemia major, or Cooley's anemia, have several features in

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Clinical Biochemical Research Section, Laboratory of Biochemistry, National Cancer Institute, National Institutes of Health.

Read before the Section on Experimental Medicine and Therapeutics at the 104th Annual Meeting of the American Medical Association, Atlantic City, June 8, 1955.

* References 3 and 4.

† References 6-10; Rucknagel, D. L.; Page, E. B., and Jensen, W. N.: Hemoglobin I: An Inherited Hemoglobin Anomaly, unpublished data; Thorup, O. A.; Itano, H. A., and Wheby, M. S.: Hemoglobin J, unpublished data.

‡ References 6-8 and 10.

§ Rucknagel, D. L.; Page, E. B., and Jensen, W. N.: Hemoglobin I: An Inherited Hemoglobin Anomaly, unpublished data; Thorup, O. A.; Itano, H. A., and Wheby, M. S.: Hemoglobin J, unpublished data.

‖ References 1 and 11-13.

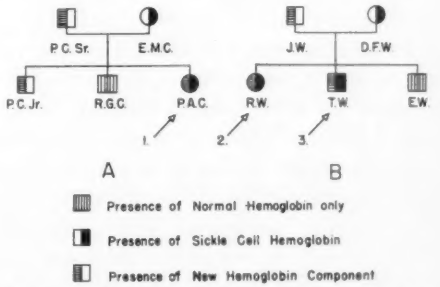


Fig. 1.—The two families in whom hemoglobin-C was first found. One parent in each family has sickle-cell trait, and the other, hemoglobin-C trait. Of the six children two are normal, one has hemoglobin-C trait, and three have sickle-cell-hemoglobin-C disease. Sickle-cell trait also appears among the offspring of such unions. (From Itano and Neel,[3] *Proceedings of the National Academy of Sciences*, Washington, D. C., The Academy.)

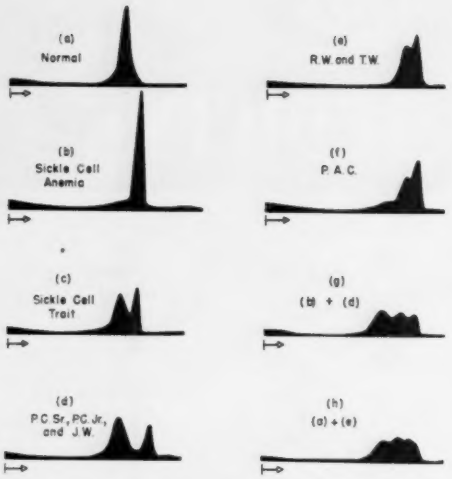
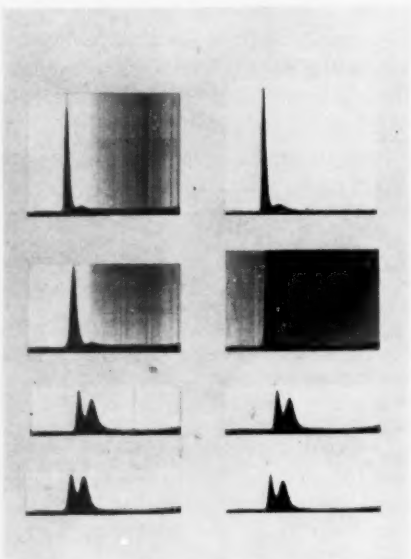


Fig. 2.—Electrophoretic patterns obtained by moving boundary electrophoresis of samples from the families represented in Figure 1. Method of Wells and Itano.[17] (*a*) Hemoglobin A only; (*b*) hemoglobin S with a small amount of hemoglobin F; (*c*) hemoglobins A and S; (*d*) hemoglobins A and C in hemoglobin-C trait; (*e*) hemoglobins S and C in sickle-cell-hemoglobin-C disease; (*f*) hemoglobins F, S, and C in sickle-cell-hemoglobin-C disease; (*g*) and (*h*) mixture experiments to demonstrate differences in mobility among hemoglobins A, S and C. (From Itano and Neel,[3] *Proceedings of the National Academy of Sciences*, Washington, D. C., The Academy.)

common. Each is characterized by a chronic hemolytic process and is refractory to treatment. Each is associated with an asymptomatic carrier state, sickle-cell trait and thalassemia minor, or Cooley's trait, respectively. In each case the carrier state is ascribed to heterozygosity in an abnormal gene and the anemia to homozygosity in the corresponding gene.[14] Studies of the physical and chemical properties of the hemoglobin molecule in these conditions have yielded much information on the nature of inherited metabolic defects in hemoglobin synthesis and have clarified the clinical aspects of sickle-cell disease and thalassemia by showing that neither is a unique entity but is a complex of diseases having similar clinical manifestations.¶

Hemoglobins of different species, while possessing many properties in common, have a number of demonstrable differences in their composition and properties. The adult hemoglobin of a given species differs from a form present in the fetus or newborn in certain physical and chemical properties.[16] The studies to be reviewed here showed for the first time that inherited abnormal forms of human hemoglobin exist and that these forms are in some cases the primary cause of anemia. Various methods are available for the characterization of proteins, and a few have been particularly effective in the detection of abnormal hemoglobins. The most useful has been electrophoresis (Figs. 2 and 3), which shows the charge difference between molecules and which permits the determination of the relative proportions of components in a mixture of differently charged molecules. Both the moving boundary and the zone

Fig. 3.—Patterns showing the similarity in the electrophoretic behavior of hemoglobins S and D. Method of Wells and Itano.[17] Left column, top to bottom, two cases of sickle-cell anemia (hemoglobin S with a small fraction of hemoglobin F) and two cases of sickle-cell trait (hemoglobins A and S). Right column, top to bottom, two cases of sickle-cell-hemoglobin-D disease (hemoglobins S and D with a small fraction of hemoglobin of F) and two cases of hemoglobin-D trait (hemoglobins A and D). The erythrocytes in hemoglobin-D trait do not sickle. The apparent difference in the direction of migration from that in Figure 2 is not due to a difference in experimental procedure. Figure 2 was prepared from tracings and Figure 3 from contact prints of the original patterns.



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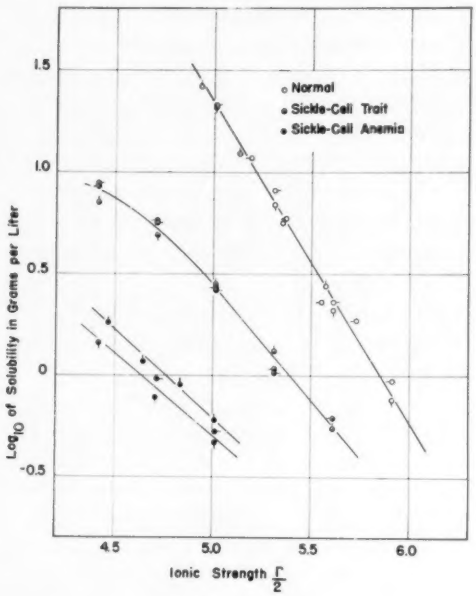

Fig. 4.—Solubilities in concentrated phosphate buffers of hemoglobins from normal adults and from persons with sickle-cell trait and sickle-cell anemia. (From Itano,[4] *Proceedings of the National Academy of Sciences,* Washington, D. C., The Academy.)

methods of electrophoresis have proved to be effective tools in hemoglobin analysis.# Salting out of hemoglobin from solutions under fixed conditions and determining its concentration in the supernatant (Figs. 4 and 5) provides a measure of the tendency of hemoglobin molecules to aggregate.* The alkali denaturation reaction (Fig. 6) and the examination of ultraviolet absorption spectra are useful methods for the detection of fetal hemoglobin.† The hemoglobins differ from each other in their globin portions,‡ but the exact nature of their difference is not known Amino acid analyses yield no significant differences in the charged amino acids.[30] Differences have been reported in the numbers of free sulfhydryl and carboxyl groups.§ Without going into detailed data, which are available in the literature, I shall review briefly the distinctive characteristics of the human hemoglobins and the various disease states with which they are associated.

References 2 and 17-24.
* References 25-27.
† References 18 and 28.
‡ References 2 and 29.
§ References 31 and 32.

NORMAL ADULT AND FETAL HEMOGLOBINS

Hemoglobin A (normal adult hemoglobin) is the only form present in measurable amounts in the majority of humans after the first six or seven months of postnatal life; consequently, it is the form present in hematologic disorders not associated with defective hemoglobin metabolism. It is also present in some of the disease states and in all of the carrier states of the hemoglobinopathies (Figs. 1-3). Hemoglobin A has an isoelectric point of 6.9 in phosphate buffer (as carbonmonoxyhemoglobin),[2] is very soluble in

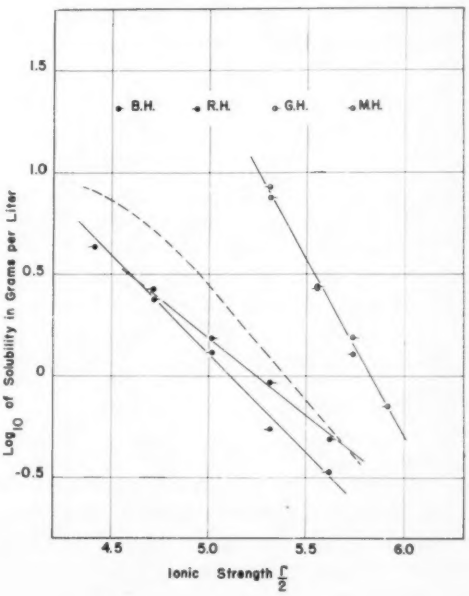

Fig. 5.—Solubilities of hemoglobin from hemoglobin-D trait (G. H. and M. H.) and from sickle-cell-hemoglobin-D disease (B. H. and R. H.). The dashed curve is the sickle-cell trait curve from Figure 4. The solubility determinations shown on Figures 4 and 5 distinguished between sickle-cell trait and hemoglobin-D trait, which yielded identical hemoglobin electrophoresis patterns, and between sickle-cell anemia and sickle-cell-hemoglobin-D disease, which also yielded identical patterns (Figure 3). (From Itano,[4] *Proceedings of the National Academy of Sciences,* Washington, D. C., The Academy.)

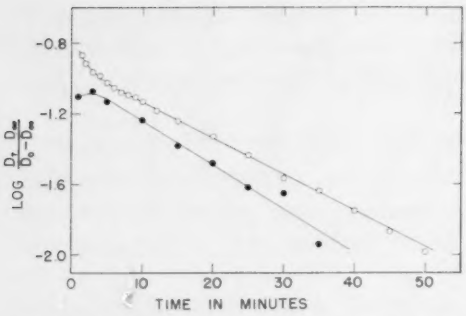

Fig. 6.—Alkali denaturation curves of a sickle-cell anemia specimen, illustrating two methods of determining the apparent percentage of fetal hemoglobin present. The ordinate is the $\log_{10}$ of the apparent fraction of undenatured hemoglobin. Open circles, modification of method of White and Beaven.[12] Filled circles, modification of method of Singer, Chernoff, and Singer.[28]

salt solutions,|| and is labile to denaturation in alkali.[28]

Hemoglobin F (fetal hemoglobin) is the first form of hemoglobin produced in the fetus. Hemoglobins A and F are present simultaneously in late prenatal and early postnatal life. The production of fetal hemoglobin persists into adulthood in many victims of hereditary anemias (Figs. 2, 3, and 6) and may occur in some victims of acquired anemias.[28] Fetal hemoglobin is distinguished from all other human hemoglobins by its elevated resistance to denaturation in alkali (Fig. 6). Its electrophoretic behavior and ultraviolet spectrum are also unique.[18]

THE ABNORMAL HEMOGLOBINS

Hemoglobin S (sickle-cell hemoglobin) differs from hemoglobins A and F in its electrophoretic behavior and solubility (Figs. 2 and 4). A calculation based on electrophoretic mobilities indicates that a molecule of hemoglobin S has about three more net positive charges than a molecule of hemoglobin A.[2] When the two hemoglobins are in the deoxygenated state, the solubility of hemoglobin S is a small fraction of that of hemoglobin A.¶ The sickling test is positive in erythrocytes containing hemoglobin S, and concentrated solutions of hemoglobin S form large molecular aggregates and gels when deoxygenated.[33] The same process, when it occurs within the red cell, causes sickling.

Hemoglobin C (Figs. 1 and 2) has a greater net positive charge than hemoglobin S and a greater solubility than hemoglobin A.# The presence of hemoglobin C is accompanied by an elevation in the percentage of target cells.*

Hemoglobin D is indistinguishable from hemoglobin S by electrophoresis (Fig. 3) but its solubility is like that of hemoglobin A (Figs. 4 and 5).[4]

Hemoglobin E is unique in that its electrophoretic mobility is similar to that of hemoglobin C on the alkaline side and to that of hemoglobin S on the acid side of their isoelectric points.† Carefully controlled moving boundary electrophoresis experiments indicate that the mobility of hemoglobin E is slightly lower than that of hemoglobin S at pH 6.5 and slightly greater than that of hemoglobin C at pH 8.6.‡

Hemoglobin G § has been reported in only one case. Its mobility by paper electrophoresis at pH 8.6 is the same as that of fetal hemoglobin, but it is labile to alkali denaturation.[9]

Hemoglobin H || has an electrophoretic mobility greater than that of hemoglobin A at pH 8.6 and an isoelectric point lower than that of hemoglobin A.¶

Hemoglobin I has an electrophoretic mobility between those of hemoglobins A and H

|| References 25-27.

¶ References 25-27.

References 5 and 27.

* References 34-36.

† References 6, 7, and 8.

‡ Itano, H. A.: Unpublished data.

§ An abnormal hemoglobin has been reported by J. D. Battle and L. Lewis, *J. Lab. & Clin. Med.* **44**:764, 1954. Its electrophoretic properties and hematologic manifestations indicate that it differs from the other abnormal hemoglobins, and it will be called hemoglobin K (personal communication from Battle and Lewis).

|| Other occurrences of hemoglobin components apparently identical with H have been observed by W. R. Bergren, H. A. Itano, and Sturgeon, and by A. G. Motulsky (personal communication to the author).

¶ Reference 10 and Itano, H. A.: Unpublished data.

at pH 8.6 and an isoelectric point between those of hemoglobins A and H.#

Hemoglobin J has an electrophoretic mobility between those of hemoglobins A and I at pH 8.6 and an isoelectric point between those of hemoglobins A and I.*

THE CLINICAL STATES

With respect to their clinical manifestations the various states characterized by inherited abnormalities in hemoglobin metabolism may be grouped into three categories, (1) the asymptomatic carrier states, (2) the sickle-cell-disease complex, and (3) the thalassemia and thalassemia-like complex.

The Abnormal Hemoglobin Traits

The conditions which come under this classification are due to the presence of a single abnormal gene, and the subjects do not under ordinary circumstances have symptoms referable to their carrier state. Their significance rests upon the fact that an offspring of the marriage of any two carriers may suffer from a chronic anemia. A hematologic examination would detect the presence of some of these conditions, but a hemoglobin analysis is necessary in the others.

Sickle-cell trait occurs in about 9% of American Negroes.[14] Sickling erythrocytes in the absence of other erythrocytic abnormality or anemia is the hematologic criterion for diagnosis. Hemoglobins A and S are present, about 25% to 45% being hemoglobin S.[17] The solubility of the mixture falls between those of hemoglobins A and S and depends on the ratio of the components.[27] Familial differences occur in this ratio.†

Hemoglobin C trait has been detected in 2% to 3% of American Negroes.‡ Hemoglobins A and C are present, usually in the approximate ratio 2:1. The solubility of the mixture is between those of hemoglobins A and C.[27] An elevated percentage of target cells occurs in this condition.§

Hemoglobin D trait is a rare condition reported in two families of European descent.‖ Hemoglobins A and D are present, and the solubility of the mixture is nearly the same as that of hemoglobin A.¶ No erythrocytic abnormality has been observed.

Hemoglobin E trait has been observed in two persons in the Western hemisphere.# It apparently has a high incidence in Thailand[39] and has also been observed in Indonesia * and in Ceylon.† Hemoglobins A and E are found in this trait. Hematologic values were found to be normal.[40]

Hemoglobin G trait has been reported in one West African person.[9] Hemoglobins A and G were present in his erythrocytes. The solubility of the mixture was the same as that of hemoglobin A. No clinical or hematologic report is at present available.‖

Hemoglobin I trait was found in three generations of an American Negro family.‡ Hemoglobins A and I were observed. The clinical and hematologic findings were negative.

Hemoglobin J trait was found in two generations of an American Negro family.§ Hemoglobins A and J were found, but other observations were normal.

Rucknagel, D. L.; Page, E. B., and Jensen, W. N.: Hemoglobin I: An Inherited Hemoglobin Anomaly, unpublished data; Itano, H. A.: Unpublished data.

* Thorup, O. A.; Itano, H. A., and Wheby, M. S.: Hemoglobin J, unpublished data; Itano, H. A.: Unpublished data.

† References 37 and 38.

‡ References 21 and 24.

§ References 34-36.

‖ References 8 and 11.

¶ References 4 and 27.

I. M. (Reference 8) and his half-sister (unpublished data).

* Lie-Injo Luan Eng: Personal communication to the author.

† Lehman, H.: Personal communication to the author.

‡ Rucknagel, D. L.; Page, E. B., and Jensen, W. N.: Hemoglobin I: An Inherited Hemoglobin Anomaly, unpublished data.

§ Thorup, O. A.; Itano, H. A., and Wheby, M. S.: Hemoglobin J, unpublished data.

‖ Since the present manuscript went to press, additional data on hemoglobin G trait and the homozygous G condition have been published by G. M. Edington, H. Lehmann, and R. G. Schneider: *Nature, London* **175**:850, 1955.

Thalassemia minor, or Cooley's trait, has been seen most often among persons from the northern shores of the Mediterranean. The erythrocytes are microcytic and have increased resistance to lysis in hypotonic saline. Normal adult hemoglobin and occasionally small amounts of fetal hemoglobin are present.

Sickle-Cell Disease

Each of the conditions in this category is characterized by hemolytic disease in the presence of sickling cells. Each is due to the simultaneous presence in the same person of two abnormal genes, and so both parents of a patient carry a hematologic abnormality. Exceptions to this rule may occur when one of the abnormalities is thalassemia || or when a mutation occurs.¶

Sickle-cell anemia is due to homozygosity in the gene for hemoglobin S; therefore each parent of a patient must show a positive test for sickling.# Hemoglobins S and F are found in this condition.* In the majority of cases the percentage of hemoglobin F is in the range 0 to 25%, but cases with as high as 40% have been observed.† The lowest solubilities of any human hemoglobin samples occur in sickle-cell anemia specimens with little or no hemoglobin F. Increasing solubilities are observed with increasing proportions of hemoglobin F.[27] The hemolytic anemia and clinical manifestations are the severest among the four types of sickle-cell disease.

Sickle-cell-hemoglobin-C disease is due to the simultaneous presence of hemoglobins S and C in nearly equal proportions.‡ Fetal hemoglobin is occasionally present in addition to hemoglobins S and C. The genes which control the production of hemoglobins S and C are probably alleles,§ and so each parent contributes one of the abnormal genes to the affected child. The solubility of the hemoglobin mixture in this condition is slightly less than that in sickle-cell trait.[27] A mild hemolytic anemia occurs, and the number of target cells is elevated.||

Sickle-cell-hemoglobin-D disease has been found in two families.¶ In each family one parent has sickle-cell trait, and the other, hemoglobin-D trait. The children with the disease have hemoglobins S and D, together with small amounts of hemoglobin F. The three cases reported to date all have mild hemolytic anemias and elevated mean corpuscular volumes. The solubility of the hemoglobin mixture is lower than that in sickle-cell-hemoglobin-C disease but higher than that in sickle-cell anemia.[27]

Sickle-cell-thalassemia disease is probably the commonest form of sickle-cell disease among Caucasians. It is due to the simultaneous presence of the genes for sickle-cell hemoglobin and for thalassemia. In the usual case one of the abnormal genes is inherited from each parent. One case in which both genes were apparently inherited from the same parent has been cited as evidence in support of nonallelism of the two genes.[41] Hemoglobins S, A, and F are present in the majority of cases,# but cases have been cited in which the hemoglobin analysis was indistinguishable from that of sickle-cell anemia, only hemoglobins S and F having been found.* The proportion of hemoglobin S is about 60% to 85%. Microdrepanocytic disease is a descriptive term for the condition, which is usually manifested by microcytic sickling cells and a mild hemolytic anemia.[41] Hemoglobin solubilities are higher than those in most cases of sickle-cell anemia but lower than those in the other two variants of sickle-cell disease.[27]

Thalassemia and Related Conditions

Wide variations in the severity of thalassemia occur among individuals and families. Recent studies have shown that some cases

|| References 41 and 42.

¶ References 14 and 43.

References 44-46.

* References 2, 28, and 47-49.

† Itano, H. A.: Unpublished data.

‡ References 36 and 38. Apparent deviations from equality have occurred when fetal hemoglobin was present in the mixture or when calculations were based on moving boundary electrophoresis diagrams with inadequately resolved boundaries.

§ References 38 and 50.

|| References 34-36.

¶ References 8 and 11.

References 36, 51, and 52.

* References 8 and 36.

previously regarded as examples of thalassemia of moderate severity are characterized by the presence of abnormal hemoglobins.[15]

Thalassemia major, or Cooley's anemia, results from homozygosity in the thalassemia gene.[14] It is characterized by severe chronic microcytic anemia and is usually fatal in childhood; however, anemias of moderate severity have been observed in apparently homozygous persons.[15] The occurrence of fetal hemoglobin is a constant finding, but its proportion may vary from 12% to nearly 100%.† The remainder of the hemoglobin is indistinguishable from normal adult hemoglobin. There is no apparent correlation between the severity of the disease and the proportion of fetal hemoglobin.[15]

Sickle-cell-thalassemia disease may be mistaken for thalassemia of intermediate severity, especially in Caucasians, if the sickling test is not done.[15]

Hemoglobin-C-thalassemia disease has been observed in three persons.‡ Hemoglobins A and C were present in two of them and hemoglobins A, C, and F in the other. Although an increased reticulocyte count was present in each, only one had marked anemia.

Hemoglobin-E-thalassemia disease is characterized by the presence of hemoglobins E and F. The clinical and hematologic manifestations are similar to those of thalassemia major of intermediate severity.§

Other syndromes involving the presence of abnormal hemoglobins are known to present some of the characteristics of thalassemia.

Hemoglobin-C disease is apparently due to homozygosity in the gene for hemoglobin C, which is the only form of hemoglobin present in nearly all cases. A small fraction of fetal hemoglobin is occasionally present. A high proportion of target cells and a mild hemolytic anemia accompany this state, which may be mistaken for thalassemia. A recent paper by Thomas and his co-workers has summarized the findings in seven cases from the literature.[56] Other reports have appeared since this summary was compiled.‖

Hemoglobin-E disease has been observed in five persons.[40] The erythrocytes were reported to be microcytic and normochromic, and 25% to 60% of them were target cells. Increased osmotic resistance to hypotonic saline was observed. Most of the hemoglobin was E, with 2% to 6% hemoglobin F.

Hemoglobin H has been found in two persons with an anemia indistinguishable from thalassemia.[10]

GENETIC RELATIONSHIPS OF THE ABNORMAL HEMOGLOBINS

The presence of an abnormal hemoglobin in a person is due to the occurrence of a mutation in one of his ancestors. A fundamental question in biochemical genetics is whether or not the abnormal hemoglobin genes are alleles, that is, whether mutations resulting in the alteration of hemoglobin metabolism takes place at one or more than one chromosomal locus. Studies of several families have furnished strong biochemical and genetic evidence that the genes for hemoglobins S and C are allelic or are closely linked.¶ There are data which indicate that these two genes are not allelic with the thalassemia gene; in each case the evidence is limited to one family.# The simultaneous presence of the genes for thalassemia and for an abnormal hemoglobin nearly always results in a relative inhibition of synthesis of normal adult hemoglobin but not of the abnormal type.* Pauling has suggested that the simplest explanation for this fact is that the thalassemia gene is allelic with the abnormal hemoglobin genes,[1] and I have suggested the possible existence of more than one isoallele for thalassemia at the abnormal hemoglobin locus.[38]

A wide diversity exists in both the clinical and the biochemical manifestations of thalassemia major and minor.[15] The two known families with hemoglobin-C-thalassemia dis-

† References 15, 53, and 54.

‡ References 42 and 55.

§ References 7, 8, and 40.

‖ References 57-59.

¶ References 38 and 50.

References 41 and 42.

* References 8, 51, 52, and 60.

ease present different biochemical manifestations. In one the thalassemia allele appears to have caused a relative inhibition of hemoglobin-A synthesis, so that there is a preponderance of hemoglobin C [42]; in the other, the synthesis of both hemoglobins A and C is inhibited, so that their ratio is the same as that in hemoglobin-C trait.[55] In contrast, the manifestations of sickle-cell trait and sickle-cell anemia (homozygous S) are remarkably constant.[36] Because of the complexity of the hemoglobin molecule, it is not unlikely that its total synthesis is under the control of more than one gene locus. The careful examination of familial hematologic and biochemical data may reveal that several genes, both allelic and nonallelic with abnormal hemoglobin locus, may produce the thalassemia effect, namely, the inhibition of hemoglobin synthesis.

RELATIONSHIP OF ABNORMAL HEMOGLOBIN METABOLISM TO ANEMIA

Two factors are involved in hemolytic disease, the production and the destruction of erythrocytes. Any person maintaining a constant hemoglobin level, high or low, is producing hemoglobin at the same rate as he is destroying it. Crosby and Akeroyd showed that anemia develops in chronic hemolytic disease when the mean life span of the erythrocytes is less than 15 to 20 days.[61] However, anemia (9.6 to 11.2 gm./100 cc.) was present in hemoglobin-C disease when the mean erythrocyte life span was observed to be as long as 30 to 55 days.[56] The slightly anemic (11.5 to 13.0 gm./100 cc.) subjects studied by Crosby and Akeroyd presumably did not carry any of the genes for abnormal hemoglobin metabolism. The mean life span of their cells was 11 to 12 days, and they produced hemoglobin at about seven times the normal rate of 0.09 gm. per kilogram of body weight per day. Despite the increased stimulus to hemopoiesis of a more severe anemia, the calculated rate of hemoglobin output in thalassemia major was only two to three times normal and in sickle-cell anemia, five to six times normal.[61]

With respect to hemoglobin production, the mutant processes thus appear to be less efficient than that controlled by the normal, or wild type, gene. This hypothesis was earlier stated on a cellular basis.[38] In the various trait conditions there is always more normal hemoglobin than abnormal in the same person. It was postulated that the proportions reflect the relative efficiencies of the synthetic processes for the normal and abnormal proteins within the same cell, the normal process being on the average about twice as fast as the abnormal ones. This hypothesis does not necessitate that the abnormal cells be hypochromic or microcytic but that these cells require a longer time to produce their normal complement of hemoglobin. It may be possible to test this hypothesis by comparing the erythroid hyperplasia of the marrow, i. e., the number of cells in production, to the degree of reticulocytosis, i. e., the rate at which cells are reaching maturation. Thalassemia major is an extreme example of retarded rate of hemoglobin synthesis. The extent of erythroid hyperplasia of the marrow is out of proportion to the rate of blood destruction,† suggesting that the period of red cell maturation is prolonged.

The increased rate of hemolysis in sickle-cell anemia has been linked directly to the presence of sickled cells in the peripheral circulation.[63] The sickling property is, in turn, due to the tendency of hemoglobin-S to aggregate when deoxygenated.[2] The primary cause of the hemolytic disease is, therefore, the synthesis within the erythrocytes of an abnormal molecular form of hemoglobin. A slight retardation in the maximum rate of hemoglobin synthesis contributes to the severity of the anemia.

Each of the two abnormal genes in hemoglobin-E-thalassemia disease inhibits hemoglobin synthesis. The thalassemia gene in this instance blocks completely the synthesis of hemoglobin A, and the hemoglobin-E gene produces an abnormal hemoglobin at a subnormal rate.[8] As in thalassemia major and sickle-cell anemia, a compensatory produc-

† References 11 and 62.

tion of fetal hemoglobin occurs. The net result is an anemia very similar in its manifestations to thalassemia major of moderate severity.

Thus, abnormal hemoglobin metabolism can result in anemia in either of two ways. An abnormal hemoglobin, the physical properties of which result in increased susceptibility to hemolysis, is the basic cause of sickle-cell disease. In thalassemia and other abnormal hemoglobin syndromes, cellular changes not ascribable to the type of hemoglobin present but which are associated with decreased erythrocyte life span take place. The rate of hemolysis is not as rapid as in sickle-cell disease, but the ability to compensate by increasing the rate of production of hemoglobin is also less.

SIGNIFICANCE OF ABNORMAL HEMOGLOBIN STUDIES

The discovery and study of sickle-cell hemoglobin provided for the first time the explanation for the manifestations of a particular disease on the basis of the physical properties of an abnormal molecule. The synthesis of this abnormal molecule is due to the presence of a mutant gene in man. A valuable experimental tool is at hand in that the existence of such a mutation is detectable by physical chemical methods. It is not necessary for this individual and a similarly affected individual to produce offspring in order to expose the abnormality. Isolation and detailed study of the abnormal hemoglobin molecules is certain to furnish us with greater insight into the effect of mutation on the structure of a protein molecule. The need for such studies becomes evident when one realizes that enzymes are proteins and could be similarly affected. It is likely that mutations which alter the structure or block the production of enzymes form the basis for other diseases, both inherited and acquired.

SUMMARY

The inherited abnormalities in human hemoglobin metabolism and the clinical states with which they are associated are reviewed. The abnormalities result in anemia by increasing the rate of erythrocyte destruction and by retarding the rate of hemoglobin synthesis so that the ability of the bone marrow to compensate for the increased rate of destruction is limited. The study of abnormal hemoglobin molecules may provide a deeper understanding of the nature of mutations in humans and of the possible bases of other disease processes.

The idea of Dr. Linus Pauling that an abnormal hemoglobin molecule might be responsible for the sickling process initiated the study of the hemoglobin molecule in hereditary anemias. S. J. Singer, J. V. Neel, I. C. Wells, E. Havinga, P. Sturgeon, and W. R. Bergren collaborated in various phases of my investigations.

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SYMPOSIUM ON PANCREATITIS

Experimental Pancreatitis

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Most of the diseases of man can be simulated experimentally in animals. Although study of the experimentally induced disease seldom provides complete and unequivocal answers to the problems of the pathogenesis of its spontaneously occurring human counterpart, such studies do give valuable information for understanding human disease processes. This they provide by disclosing basic mechanisms of alteration of structure and function. From these we can frequently make useful hypotheses about the nature of the derangement in human disease.

In the example at hand, pancreatitis, all of the major features of the various forms of the human disease can be relatively faithfully mimicked by experimental procedures in animals. This presentation addresses itself to the task of (*a*) setting forth, insofar as they are known, the basic mechanisms in the pathogenesis of the experimental disease and (*b*) evaluating critically the possible applicability of these in the human disease. A comprehensive review of the literature on experimental pancreatitis will not be undertaken here (see Ivy and Gibbs [1] for a recent review of the subject).

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PHYSIOLOGY OF PANCREATIC SECRETION

The main regulation of pancreatic secretion is accomplished by hormones formed by the mucosa of the upper portions of the small intestine.[4] Secretin is released in response to the presence of acid, amino acids, and digestion products of fat, in this order of effectiveness. It stimulates the secretion of water and bicarbonate, leaving the rate of secretion of enzymes unaltered. Amino acids, soap, and acid, in this order of effectiveness, cause release of pancreozymin, which stimulates secretion of enzymes by the pancreas and has no effect on water and bicarbonate secretion. The digestive enzymes are secreted by the acinar cells; the water and bicarbonate probably come from the intralobular ducts, including the portion which extends into the acini as centroacinar cells. Cholinergic impulses from the vagus nerves stimulate mainly enzyme secretion, with little effect on volume of juice. They also cause contraction of the smooth muscle of the ducts. The sympathetic nerves to the pancreas have a weak cholinergic and a strong adrenergic component. The former produces effects like vagal stimulation; the latter results in constriction of small blood vessels.

HISTOPATHOLOGY OF PANCREATITIS

The essential histopathologic features of acute pancreatitis, both in the experimental animal and as it occurs spontaneously in man, are edema and inflammatory cellular infiltration of the interstitial spaces, necrosis and disintegration of acinar cells, intrapancreatic and extrapancreatic fat necrosis, and hemorrhage from necrotic vessels. These

have been listed in order of increasing severity of the process; all gradations may be seen in both the experimental and the human disease. Edema, inflammatory cellular infiltration, and parenchymal necrosis are common expressions of inflammatory processes in all organs. Fat necrosis and the peculiar variety of vascular necrosis with hemorrhage are distinctive and unique features of pancreatitis.

Fat necrosis is caused by the action of pancreatic lipase on the triglyceride of fat-storage cells. Fatty acid released by the enzymatic hydrolysis of neutral fat combines with calcium from blood and tissue fluid to form calcium soaps. The replacement of neutral fat by calcium soaps and fatty acid crystals and the attendant inflammatory reaction produce the characteristic gross and microscopic picture of fat necrosis.

Hemorrhagic necrosis is produced by the action of the proteolytic enzymes of the pancreas, trypsin and chymotrypsin, on blood vessels. Necrosis of the vessel wall with rupture and hemorrhage is the sequence of events. Rich and Duff [2] demonstrated that subcutaneous injection of solutions of crystalline trypsin or chymotrypsin would reproduce this vascular lesion locally just as it occurs in pancreatitis.

These distinctive lesions occur when the concentration of the respective pancreatic enzymes in the interstitial spaces becomes sufficiently high. The lesions may be confined to the pancreas or they may involve contiguous structures or they may be widespread throughout the abdominal cavity when adequate quantities of activated enzymes enter the peritoneal cavity.

ENTRY OF PANCREATIC ENZYMES INTO TISSUE SPACES

The mode of entry of pancreatic enzymes into tissue spaces is not completely understood. In the normal intact pancreas some passage of enzymes from the acinar cells, where they are formed, into the blood occurs. Presumably this is due to a slight degree of "endocrine" secretion of a predominantly exocrine product, a process known to occur for other digestive enzymes.[3] Thus, pancreatic amylase and lipase are always normally present in blood plasma. There is good evidence to indicate that these enzymes do not enter the blood by reabsorption from the ducts or from the intestine after secretion. This would imply that small amounts of the enzymes normally leave the end of the acinar cells opposite the gland lumen and traverse the interstitial spaces in going from acini to blood.

In the presence of obstruction to the outflow of pancreatic juice from the ducts, the passage of enzymes into the interstitial spaces and consequently into the blood is markedly accelerated. Increase in hydrostatic pressure within the ducts would appear to be the immediate cause of the increased passage of enzymes into the blood. Thus, secretin, a hormone which stimulates secretion of water and bicarbonate but not of enzymes [4] will, in the presence of obstruction, cause a rise in serum enzymes.[5] Similarly, a rise in intraductal pressure produced by cannulation of the duct and attaching it to a manometer of saline will cause elevation of serum enzymes even when the pressure used is below the maximum secretory pressure of the pancreas.[6] In human subjects reflux of contrast medium into the pancreatic duct from a tube in the common bile duct produces elevation of serum enzymes even when pressures no higher than 20 to 30 cm. of water are attained.[7] Conversely, parasympathomimetic agents, which stimulate enzyme secretion, produce elevation of serum amylase in dogs only when occlusion of the pancreatic duct by spasm of the sphincter is permitted to occur. When obstruction is prevented by placing a cannula in the sphincter, the rise in serum amylase is prevented.[8] Thus, the evidence indicates that neither increase in volume flow of pancreatic juice nor stimulation of pancreatic enzyme production per se cause an increase in serum enzymes but that elevation of intraductal pressure is the determining factor. However, stimulation of flow in the presence of obstruction can

produce elevation of intraductal pressure, and stimulation of enzyme production in the presence of increased intraductal pressure can augment the rise in serum enzymes.

It is sometimes hypothesized that the elevation of serum enzymes with rise in intraductual pressure is due to disruption of the acinar cells, allowing the pancreatic juice to flow in retrograde fashion between them. However, elevations of intraductal pressure too low to produce any histologic alteration can produce marked elevation of serum enzyme levels. This would appear to be merely an accentuation of the normal process of "endocrine" secretion of enzymes. Although pronounced elevation of serum enzymes can be produced without histologic evidence of damage to acinar cells, the occurrence of local damage from enzyme action is usually seen only in the presence of necrosis of acinar cells. This suggests that the enzymes in interstitial fluid reach concentrations adequate to produce local damage only when disruption of acinar cells and spilling out of the contained enzymes takes place. This is admittedly a speculative point of view and has not been rigidly established by experiment.

Fat necrosis frequently occurs without hemorrhagic necrosis, indicating that the mechanisms protective against digestion of tissue by the proteolytic enzymes of the pancreas are more effective than those acting to counteract lipolysis. Lipase is secreted in the active form by acinar cells. Juice of low enzyme concentration, too weak to produce hemorrhagic necrosis even when the proteases are activated, will, when injected subcutaneously, produce fat necrosis.[2]

ACTIVATION OF PANCREATIC PROTEASES

Trypsin and chymotrypsin are secreted as inactive precursors, trypsinogen and chymotrypsinogen.[9] The normal process of conversion of trypsinogen to trypsin occurs in the intestinal lumen, where an enzyme secreted by the intestinal mucosa, enterokinase, catalyzes this transformation. The process is also autocatalytically promoted; that is, trypsin acts enzymatically to convert trypsinogen into trypsin. The conversion of chymotrypsinogen into its active form is accomplished enzymatically by trypsin. A small portion of the protease of pancreatic juice is sometimes present in active form in the pancreatic ducts. The frequency with which this occurs is increased when the juice has a high enzyme concentration.[10] It has not been determined whether this protease is trypsin, chymotrypsin, or both.

Both the pancreatic gland and the pancreatic juice contain a low-molecular-weight protein which is a specific inhibitor of trypsin.* The trypsin inhibitor combines stoicheiometrically with trypsin to form a trypsin-inhibitor complex which is enzymatically inert. Trypsin inhibitor also decreases the rate of transformation of trypsinogen to trypsin. The amount of trypsin inhibitor in pancreatic juice is sufficient to combine with only a small portion of the trypsin (after conversion from trypsinogen) in pancreatic juice. When active protease is found in pancreatic duct juice, it must be presumed either that trypsin is present in active form in excess of the amount of trypsin inhibitor or that the protease is chymotrypsin, a problem awaiting solution. In the intestinal lumen trypsin inhibitor is inactivated, possibly by enterokinase.[12]

It is evident that mechanisms exist to prevent activation of pancreatic proteases before they reach the intestine. In hemorrhagic pancreatitis these mechanisms are overcome and proteolytic digestion of tissues occurs. It is frequently stated that when pancreatic juice gains access to interstitial spaces activation of proteases can occur by a variety of means other than action by enterokinase. Thus it has been claimed that bile, inflammatory exudates, normal tissue juices, and calcium ions in the concentration present in interstitial tissue fluid can bring about activation of the proteases.[13] Unfortunately, most of these statements are based upon qualitative experiments performed before the era of modern quantitative enzymology. It is true that autoactivation of pancre-

* References 11 and 12.

atic proteases can occur under a variety of circumstances, but it has not been rigidly proved whether this occurs whenever pancreatic juice enters tissue spaces or whether special factors must be present to produce or accelerate activation. The subcutaneous injection of pancreatic duct juice will produce hemorrhagic necrosis if the juice is high in enzyme concentration.[2] It has not been determined whether this effect is due to active enzyme which might have been already present in the juice or to activation of the proteases after injection. These are important problems for future study.

ENTRY OF THE PANCREATIC PROTEASES INTO BLOOD

Under normal conditions, trypsinogen and chymotrypsinogen would be expected to enter the blood in the same manner as amylase and lipase. The presence of these protease precursors in blood has not been demonstrated. The problem is not easy to solve, because blood plasma contains relatively potent inhibitors of these enzymes and also because plasma contains other proteases not easily distinguishable from the pancreatic proteases, notably plasmin.[14] In hemorrhagic pancreatitis the pancreatic proteases become activated and produce local tissue damage. It must be assumed that having gotten into the tissue spaces they then pass into the blood. Although, because of the protease inhibitors in plasma, moderate amounts of these proteases can be tolerated when injected intravenously and indeed one of them, trypsin, has been recommended for therapeutic use,[15] larger amounts produce profound shock and, when the amount is sufficient, death.[16]

In recent years some investigators † have addressed themselves to the problem of the possible role of circulating active protease in the shock and death which attend severe pancreatitis. The evidence is neither abundant nor clear-cut. In severe experimental pancreatitis a rise in plasma protease activity (after separation from the protease inhibitors) has been demonstrated,[14] but it has not been proved that this is pancreatic in origin. The use of purified soybean trypsin inhibitor in the treatment of experimental pancreatitis has given equivocal results.‡ In the study in which this treatment did not produce reduction in mortality [17] much smaller doses were used than in the study in which counteraction of the hypotension of acute experimental pancreatitis was demonstrated.[14] The changes in blood clotting factors found in clinical and experimental pancreatitis,§ although resembling those seen after intravenous administration of trypsin,[20] could be due to other factors.

METHODS FOR PRODUCING PANCREATITIS EXPERIMENTALLY

The following factors have been found to be capable of producing some degree of damage to the pancreas experimentally: (*a*) obstruction of the ducts, especially when accompanied by stimulation of secretion; (*b*) impairment of blood supply; (*c*) mechanical or chemical trauma, and (*d*) metabolic interference with the function of the acinar cells.

Obstruction of Pancreatic Ducts.—The degree and kind of damage seen in the pancreas after obstruction of the ducts varies with species of animal and degree of stimulation of the pancreas in the early period of obstruction. In rats [21] partial or complete obstruction of the ducts produced edema, inflammation, degeneration and atrophy of acini, and intrapancreatic and extrapancreatic fat necrosis. There was no significant degree of pancreatic parenchymal necrosis or hemorrhagic necrosis. The results were unaltered by the presence or absence of access of bile to the obstructed pancreas. Stimulation of the pancreas with food or drugs did not alter the results. In cats [22] ligation of the ducts alone produced edematous pancreatitis. When stimulation of secretion by food or drugs accompanied obstruction, pancreatitis of various degrees of severity resulted, including acinar necrosis, severe fat

† References 14, 17, and 18.

‡ References 14 and 17.

§ References 18 and 19.

necrosis, and minimal hemorrhagic necrosis. In dogs [23] ligation of the ducts plus stimulation by injection of secretin produced marked edematous pancreatitis but no fat or vascular necrosis. In rabbits [24] ligation of the pancreatic duct produced relatively little inflammatory reaction, the major changes being atrophy and disappearance of acinar cells, dilatation of intralobular ducts, and interlobular fibrosis. Fat necrosis and hemorrhagic necrosis were not seen in spite of the fact that the animals had stimulation of pancreatic secretion from feeding. In all species prolonged obstruction of the ducts eventually leads to atrophy and disappearance of the acinar cells. When the disintegration of acinar cells is very rapid fat necrosis may occur. These findings suggest that the determining factor in the occurrence of fat and hemorrhagic necrosis is the rate at which the acinar cells disintegrate. When the breakdown of acinar cells is slow no fat and hemorrhagic necrosis occurs; when breakdown is rapid these necrotic lesions may appear, but vascular necrosis with hemorrhage occurs only with fulminating disintegration.

The degree to which obstruction of the ducts occurs in human pancreatitis is debated.‖ An obvious source of obstruction, such as a gallstone obstructing the common papilla of the bile and pancreatic ducts, is seldom found. Rich and Duff [2] believed that metaplasia of the ductal epithelium was a frequent cause of obstruction in human pancreatitis, but later workers have seldom commented on the presence of this lesion. Perhaps the most distinctive histologic evidence for the existence of obstruction is dilatation and thinning of the epithelium of the intralobular ducts. These can be specifically stained by the alkaline phosphatase technique.[26] A study of the presence of this feature in necropsy and biopsy material from human pancreatitis should prove instructive.

The frequent history of a large meal preceding an attack of acute pancreatitis ¶ suggests that stimulation of pancreatic secretion may, in some instances, play an important role in the pathogenesis of the human disease.

Impairment of Blood Supply.—In dogs [25] transient interference with the arterial blood supply to the pancreas will, when accompanied by obstruction of the ducts, lead to massive necrosis of the parenchyma of the gland and the appearance of hemorrhagic necrosis in addition to the features already mentioned under the effects of obstruction. There is no evidence to indicate that impairment of blood supply occurs with significant frequency as an initiating factor in human pancreatitis.[1]

Mechanical and Chemical Trauma.—The most popular method for the experimental production of pancreatitis is one first used by Claude Bernard,[27] namely, forcible injection of bile into the pancreatic ducts. This leads to rupture of acini and severe, usually fatal, pancreatitis with extensive fat and hemorrhagic necrosis. It can be shown that both mechanical and chemical trauma play a role in the pathogenesis of this form of experimental pancreatitis. That mechanical trauma is involved is demonstrated by the fact that only mild transient inflammation of the gland occurs if the bile enters the pancreas under physiological pressures.[28] That chemical trauma is involved is shown by the fact that forcible injection of saline rather than bile again produces only mild and transient changes.[2] The chemical irritant in bile has been shown to be the bile salts. Other chemical irritants, e. g., acids and alkalis, produce effects similar to those of bile.[2]

Can pressures of the magnitude required to produce this experimental lesion occur spontaneously? The known factors which could contribute to rise in intraductal pressure in the pancreas are the secretory pressures of the liver and pancreas and the pressure which can be produced by contraction of the gallbladder (the biliary factors could operate only in the presence of a "common channel"). None of these pressures is great enough to approach the pressures

‖ References 1 and 2.

¶ References 1 and 2.

attained by forcible injection experimentally.[1] It has been suggested that the elevated pressures which develop during vomiting might contribute to the pathogenesis of human pancreatitis. However, under these circumstances there is a generalized increase in intra-abdominal pressure and it is doubtful whether a pressure differential sufficient to rupture the pancreatic ducts could be produced by such a mechanism. Furthermore, Mann and Giordano [28] found that pressures higher than those encountered during vomiting were required to produce the experimental disease.

The smooth muscle of the intramural portion of the pancreatic duct might be thrown into spasm either by extension of inflammation from the biliary tract or by reflex effects even when a common channel does not exist. This would produce only obstruction.

The experimental evidence does not support the hypothesis that hemorrhagic necrosis could result from simple obstruction of the ducts or from reflux of bile into the pancreatic ducts under physiological pressures. The frequent association of biliary tract disease with pancreatitis is a well-established clinical fact. That this association depends mainly upon a reflux of bile into the pancreas through a common channel or upon obstruction of the pancreatic duct is open to considerable doubt.

Metabolic Factors.—The pancreas is one of the most active tissues in the body in regard to protein synthesis. Dietary imbalance involving protein deficiency can lead to abnormality of pancreatic function and histopathologic changes in the pancreas both experimentally # and clinically.[35] The histologic changes consist mainly of atrophy of the acinar cells with varying degrees of fibrosis, although in the one study reported on dogs [32] moderate degrees of fat necrosis were encountered.

Recently an important new tool for the experimental study of pancreatic function and dysfunction has come into use in the form of an analogue and antimetabolite of methionine, namely, ethionine. Feeding or injection of ethionine produces pancreatic lesions in animals.* These vary from atrophy of the gland to severe pancreatitis with fat and hemorrhagic necrosis, depending upon the dosage schedule of administration. Once again, support is given to the hypothesis that the rapidity of disintegration of the acinar cells will determine whether the "hallmark" lesions of fat and hemorrhagic necrosis will appear or whether simple atrophy results.

Injection of a single large dose of ethionine into dogs [42] produces impairment of pancreatic enzyme secretion without suppression of volume flow and without histologic damage. This effect is reversible by the simultaneous injection of an equimolar amount of methionine. Presumably the continued existence of this metabolic impairment of enzyme protein synthesis eventually leads to degeneration of the acinar cells. When doses of ethionine which will eventually produce severe necrosis of the gland are given daily, there is a fall in serum amylase during the first few days, followed by a transient elevation and a return to subnormal levels. The transient elevation corresponds to the period when maximal rate of disintegration of acinar cells is seen histologically.†

In the presence of ethionine pancreatitis the ratio of trypsin inhibitor to total protease becomes lowered in both pancreatic tissue and pancreatic juice and the frequency of occurrence and concentration of active protease in the duct juice is increased.[41] These findings suggest that an impairment of the mechanism which normally prevents activation of pancreatic proteases before they reach the intestine may be involved in the pathogenesis of this form of pancreatitis. A similar tendency for the occurrence of increased amounts of active protease has been reported [48] for pancreatic juice collected by duct cannulation in patients with acute pancreatitis.

References 29-34.

* References 36-41.

† References 39 and 40.

ALCOHOL

The incidence of acute and chronic alcoholism in patients with pancreatitis is high.[44] The possible mechanisms by which alcohol ingestion might lead to pancreatitis include (*a*) stimulation of pancreatic secretion, (*b*) obstruction of the pancreatic ducts by inflammatory duodenitis involving the papillae of the ducts, and (*c*) abnormality of protein metabolism.

Although earlier workers claimed that alcohol stimulates pancreatic secretion, more recent studies ‡ have failed to confirm this. Aside from the stimulation secondary to that of gastric acid secretion, alcohol does not stimulate pancreatic secretion, neither by causing release of secretin from the intestinal mucosa nor by a direct action on the pancreas.

That gastroduodenitis frequently occurs in association with acute and chronic alcoholism is a well-known fact. Whether this could lead to inflammatory obstruction of the pancreatic ducts remains a speculative possibility. None of the pathologic studies on pancreatitis associated with alcoholism have made specific observations on this feature. It would be desirable to gather information on this point.

The role of abnormal protein metabolism in the pancreatitis associated with alcoholism is also a hypothetical possibility. It has not been established on the basis of specific studies directed to this end. The clinical literature indicates that acute alcoholism, with or without chronic alcoholism, is most frequently associated with acute pancreatitis. This would speak against an effect on protein metabolism as the major mechanism of pancreatic injury by alcohol. On the other hand, subacute and chronic pancreatic lesions are frequently encountered in association with chronic alcoholism with or without cirrhosis of the liver.§ The possibility must be entertained that altered protein metabolism plays a role in the production of these subacute and chronic lesions and that they predispose to acute pancreatitis.

‡ References 44-46.

§ References 1 and 44.

PANCREATIC SECRETION IN EXPERIMENTAL PANCREATITIS

If the hydrostatic pressure against which the pancreas is secreting is gradually elevated, suppression of secretion does not begin to occur until pressures near the maximal secretory pressure are reached.[47] From this we may assume that in the presence of obstruction the intraductal pressure will quickly rise to the maximal secretory pressure (30 to 40 cm. of water) and will remain at this level until the continued exposure to this pressure causes the gland to lose its ability to secrete. Complete obstruction of the ducts in rabbits [24] leads to rapid decrease in the response to secretin and pancreozymin. At the end of four days these responses are reduced to about 20% of the control values. A slower rate of decline then ensues, with enzyme response abating more rapidly than volume response. At the end of 14 days a minute volume response may be obtained but the juice is almost devoid of enzymes.

After forcible injection of bile into the pancreatic ducts of dogs [48] impairment of secretion is maximal immediately and involves both volume and enzyme production. If the damage produced is moderate, complete histologic and functional recovery occurs over a period of weeks. If severe damage is produced, recovery may be slow and incomplete or absent, in which instance extensive replacement fibrosis is found in the gland.

In dogs with ethionine-induced pancreatitis ‖ impairment of secretion is maximal at the time when serum enzyme levels show a transient rise and histologic changes are maximal. Enzyme secretion is depressed to a somewhat greater extent than is the volume of juice. If damage has not been severe, complete recovery of secretory function may occur when administration of ethionine is discontinued.

It is seen that all types of experimental pancreatitis produce impairment of pancreatic secretion with a tendency for greater suppression of enzyme production than of

‖ References 39-41.

volume of juice. To some extent the decreased functional capacity of the injured pancreas can be looked upon as a protective mechanism, tending to limit further damage.

AN OUTLINE OF FACTORS CONTRIBUTING TO NECROSIS

The digestive enzymes of the pancreas are formed in the zymogen, or acinar, cells of the gland and, under normal circumstances, are discharged mainly into the lumen of the ducts and conducted to the intestine. Small amounts of enzymes also enter the interstitial fluid and thus gain access to the lymph and blood. When larger amounts of enzymes are present in the interstitial fluid, they may produce necrosis of tissue. Some of the factors which may operate to determine whether necrosis will occur are the following:

A. Factors influencing the entry of enzymes into the interstitial spaces
   (*a*) Increased intraductal pressure
   (*b*) Disintegration of acinar cells with discharge of the contained enzymes
B. Factors influencing necrotic potency of juice
   (*a*) Amount of juice entering interstitial spaces
   (*b*) Concentration of enzymes in juice
   (*c*) State of activation of proteases in juice
C. Factors influencing the resistance of tissues to the necrotic action of pancreatic juice
   (*a*) Blood supply
   (*b*) Damage to tissue by trauma, chemical agents, or metabolic derangements.

SUMMARY AND CONCLUSIONS

Experimental studies in animals have demonstrated that the distinctive histopathologic lesions of pancreatitis are due to the action of pancreatic enzymes which have gained access to the tissue spaces of the pancreas and to the peritoneal cavity, have become activated, and have digested tissues. Experimentally this sequence of events can be initiated by several factors acting in concert, including obstruction of the pancreatic ducts, stimulation of pancreatic secretion by drugs or food, and interference with the blood flow to the gland. A combination of mechanical and chemical trauma, forcible injection of chemical irritants into the pancreatic duct, also produces fulminating pancreatitis. The picture of hemorrhagic pancreatic necrosis can also be induced experimentally by administration of the amino acid ethionine, an analogue and antimetabolite of methionine, which causes necrosis and disintegration of the zymogenic cells of the pancreatic acini.

After consideration of the possible role of these factors in the human disease it is concluded that, although some of them can be shown to be present in some cases, in most instances it is not possible to reconstruct the process on the basis of the experimentally studied factors.

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ABSTRACT OF DISCUSSION

Dr. James L. A. Roth, Philadelphia: We are indebted to Dr. Grossman for this very lucid review of the physiology of the pancreas as applied to pancreatitis. The concept of an "endocrine" secretion of the predominantly exocrine pancreatic enzymes provides us with an understanding of (1) the presence of amylase and lipase normally in the serum and (2) the elevation of these serum enzymes in the presence of obstruction to the egress of pancreatic juice from the duct, particularly with concomitant stimulation of pancreatic secretion.

The demonstration of the presence of a small amount of active protease in pancreatic juice within the duct enables us to explain the proteolytic digestion of hemorrhagic necrosis. Both (active protease and necrosis) are apparently seen more frequently when pancreatic juice has a high enzyme concentration, which is more apt to occur after a large meal, with or without the added stimulus of increased gastric acid (secretin) provoked by alcoholic indulgence. Thus, the occurrence of acute pancreatitis following an especially large meal, which stimulates vagal, secretin, and pancreozymin mechanisms, implicates the volume rate of pancreatic secretion in the pathogenesis.

The variation in results of ligation of the pancreatic duct in different animal species again suggests caution in the unqualified application of such experiments to man. Although the experimental pathologic lesions appear identical to those encountered in man, such evidence does not constitute proof that they are related pathogenically.

Obstruction to the outflow of pancreatic juice appears to be a common denominator in the methods for experimental production of pancreatitis, except in metabolic or ethionine-induced pancreatitis. Such evidence has fostered the "common channel" theory, whether that obstruction be due to stone, spasm, or edema. Spasm of the sphincter of Oddi and/or the duodenal musculature can produce pressures of 60 to 70 cm., which may well exceed the secretory of pressure of the pancreas and force bile into the pancreatic duct via a "common channel." Bile salts may thus gain access, damage cellular membrane, and cause disintegration of acinar cells. However, reflux of bile is not an absolute essential, and obstruction may occur to the pancreatic duct alone as the result of pancreatic calculus or calcinosis, duodenal spasm with compression of the intramural portion of the pancreatic duct, and edema or spasm of the pancreatic duct alone.

The experimental production of pancreatitis with a protein-deficient diet, or ethionine-induced deficiency of methionine, provides a new approach to the pathogenesis. It suggests an understanding of the pancreatic fibrosis and resultant pancreatic insufficiency seen in association with malnutrition of kwashiorkor, chronic alcoholism, nutritional-alcoholic type of cirrhosis of the liver, and as a secondary feature in the malnutrition of "sprue" and ulcerative colitis. If the alcoholic type of pancreatitis in man is due to an associated chronic protein deficiency similar to that induced by ethionine, some additional factor would have to be postulated to account for the abruptness in onset of the disease as encountered clinically. The changes produced in experimental animals develop gradually over a period of one to several weeks.

An understanding of the pathogenesis of acute pancreatitis is essential to and determines the rationale of therapeutic measures. Thus, if we believe in the "common channel" mechanism we might anticipate success in preventing recurrent attacks of pancreatitis, when it is associated with biliary tract disease, following cholecystectomy and/or sphincterotomy. However, such a common communication need not be implicated in the alcoholic type of pancreatitis, and these surgical procedures would not be expected to yield as good results. Perhaps the speakers to follow will shed some additional light on this aspect. Clinical experience has certainly indicated the necessity of total abstinence from alcohol in the prevention of recurrent attacks of acute pancreatitis apparently due to the imbibition of alcohol.

A question which has always puzzled me is "Why do we encounter acute pancreatitis so relatively infrequently, when acute overindulgence in alcohol is so relatively common?" I suspect that this is the basis for considerable rationalization and comfort on the part of most of us at one weak moment or another.

Clinical Features of Acute Inflammation of the Pancreas

Analysis of Ninety-Four Attacks in Seventy-Eight Patients

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This report is based on a study of 78 patients admitted to the Graduate Hospital with the diagnosis of primary acute pancreatitis or recurrent acute pancreatitis. Since several patients were admitted more than one time, there are a total of 94 separate admissions between 1941 and 1954. Unfortunately, not all patients with this diagnosis during these years could be used, because of inadequate objective data in some of the charts of patients seen in the earlier years. The incidence of acute pancreatitis has been increasing progressively in recent years, with 50% of the patients herein reported being admitted during the years 1952-1954. In part, this may be the result of a greater awareness of the disease and the more frequent employment of the serum pancreatic enzyme determinations.

The purpose of this study was to evaluate the cumulative clinical experience with acute pancreatitis. Consideration has been given to a critical appraisal of etiologic factors, significant clinical manifestations and laboratory findings, pancreatic serum enzyme behavior correlated with clinical and other laboratory data, the assistance provided by x-ray studies, the difficulty in establishing a clinicopathological correlation (necrosis versus edema), and the results of therapy. The late manifestations of recurrent pancreatitis and of pancreatic insufficiency will not be considered here.

ETIOLOGY

Regardless of the precise mechanism involved, it is generally admitted that acute nontraumatic pancreatitis occurs most frequently in association with biliary tract disease or excessive imbibance of alcohol.[1]

Biliary tract disease associated with pancreatitis was present in 36 patients (39 admissions), while 31 patients (41 admissions) gave a history of significant alcoholic intake (Table 1). In eight of the patients in the alcohol group there was no history of alcohol having been ingested immediately prior to the attack, while in seven patients there was no definite history of chronic alcoholism. The

TABLE 1.—*Etiology*

	Patients, No.	Admissions
Alcohol*	31	41
Biliary tract disease	36	39
Surgical trauma	3	3
Allergy	1	1
Probably alcohol	2	3
Probably biliary tract disease	2	2
Unknown	3	5

* One patient in the alcohol group had a calculus in the main pancreatic duct.

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diagnosis of biliary tract disease was based on surgical findings in 23 cases and on x-ray studies in 13. A certain number of patients unquestionably had acute cholecystitis, and in others there was no reasonable doubt concerning the concomitant presence of biliary colic without acute cholecystitis. In most cases the elective operation for concomitant biliary tract disease was so delayed that it was not possible to decide in what proportion of patients acute severe cholecystitis occurred simultaneously with the acute inflammation of the pancreas. It is of some interest that 9 of 23 patients who eventually had elective biliary tract surgery had choledochal pathology (Table 2). This is a higher incidence than we find in surgery for cholelithiasis without pancreatic disease. Two patients in the alcohol group had cholelithiasis, but in these patients the pancreatitis was considered to be more closely related to alcohol ingestion. One of the patients included in the alcohol group had a stone in the main pancreatic duct. This was removed, but postoperative pancreatitis recurred and diffuse calcinosis developed. One or the other of these two factors, i. e., excessive imbibance of alcohol or biliary tract disease, was noted in 86% of patients with acute pancreatitis. In two additional patients there was nonvisualization of the gall bladder on one examination, done within two weeks of the acute episode. Two others were suspected of being alcoholic, but the history was inconclusive. If these are included, then biliary tract disease or overindulgence in alcohol were probably concerned with the occurrence of pancreatitis in 91% of the entire group.

TABLE 2.—*Diagnosis of Biliary Tract Disease in Thirty-Six Patients*

	Cases, No.
I. Surgical diagnosis	23
A. Cholelithiasis without common-duct involvement	14
B. Cholelithiasis with common-duct involvement	9
(1) Stones	4
(2) Dilated without stones	4
(3) Thickened	1
II. X-ray diagnosis	13
A. Cholelithiasis	8
B. Nonfunctioning gall bladder	5

Three patients experienced acute pancreatitis immediately after abdominal laparotomy. In two of these a subtotal gastric resection had been done for duodenal ulcer. In each instance the ulcer was adherent to the pancreas and an attempt had been made to resect the ulcer. In the other instance of postoperative pancreatitis, an attempt had been made to remove a peri-Vaterian duodenal diverticulum, embedded in the head of the pancreas. One instance of recurrent acute pancreatitis was believed to be on an allergic basis. In one patient, who was not included in this series because of incomplete records, acute pancreatitis was the initial symptom of carcinoma of the pancreas. In the remaining three patients, no definite etiologic factor was established.

ADMISSION DIAGNOSIS

A review of these cases confirms our previous impression that it is rarely possible to make a definite diagnosis of acute pancreatitis solely by bed-side examination. Almost all experienced clinicians admit that acute pancreatitis follows no consistent symptom pattern, that it masquerades in many different guises. It is not our purpose in this presentation to review the salient clinical configurations encountered.[2]

The admission diagnoses were correct in 54 cases (57%) and incorrect in 40 cases (43%). The disease most commonly mistaken for acute pancreatitis was biliary tract disease, including acute cholecystitis, cholelithiasis, or choledocholithiasis. The majority of patients in which these diagnoses were made did have biliary tract disease as well as pancreatitis, although in several instances (3 of 18) the biliary tract was normal and the only lesion was acute pancreatitis. Other common erroneous diagnoses were perforated viscus and intestinal obstruction. In those cases labeled "intestinal obstruction," the predominant clinical finding was distention, and the films of the abdomen were consistent with this diagnosis. Four alcoholic patients were seen in the emergency ward with nausea, vomiting, diarrhea, and abdominal pain. Because of the strong alcoholic history, the

diagnosis of alcoholic gastritis or gastroenteritis was made. Routine serum enzyme studies, however, were elevated. There were five patients in whom the initial diagnosis was "pelvic disease," including pelvic inflammatory disease, ruptured tubo-ovarian abscess, and ectopic pregnancy. In all of these patients, the predominant site of pain was the left middle and lower abdomen. Two patients were admitted with a diagnosis of acute myocardial infarction. However, one patient died 36 hours after admission and necropsy showed no evidence of acute myocardial disease. One patient was explored with the diagnosis of acute appendicitis, and the appendix was normal. Subsequent necropsy disclosed an acute hemorrhagic pancreatitis (Table 3).

TABLE 3.—*Admission Diagnoses*

Diagnosis	Cases	
	No.	%
Correct (acute pancreatitis)	54	57
Incorrect		
(a) Acute cholecystitis	18	20
(b) Perforated viscus	6	7
(c) Intestinal obstruction	5	5
(d) Acute gastroenteritis	4	4
(e) Pelvic disease	4	4
(f) Acute coronary occlusion	2	2
(g) Acute appendicitis	1	1
Total	40	43

CLINICAL ASPECTS

For purposes of discussion of the clinical features presented by these patients, we have continued to segregate the cases into the two main groups based on etiology, i. e., into alcohol and biliary tract groups. We hope to be able to determine whether or not a difference exists in the clinical and pathological behavior of acute pancreatitis in these two groups of patients.

Age.—The youngest patient was 19; the oldest was 87 years of age. A difference was noted between the alcohol and the biliary tract disease groups. The average age of the former was 40, and that of the latter was 50 years. Over 80% of the alcohol group were 50 years of age or less, while the ages of the biliary tract group were fairly equally distributed through the third to the seventh and eighth decades.

TABLE 4.—*Sex Distribution*

	Male				Female			
	Admissions		Patients		Admissions		Patients	
	No.	%	No.	%	No.	%	No.	%
Biliary tract	19	32	16	36	20	57	20	58
Alcoholic	30	51	21	48	11	31	10	30
Miscellaneous	10	17	7	16	4	12	4	12
Total	59		44		35		34	

Sex.—This disease was seen slightly more frequently in males. Forty-four males had a total of 59 admissions for pancreatitis, while there were 35 admissions in 34 females. Alcoholism was the major etiologic factor in males, whereas the majority of the females had concomitant biliary tract disease (Table 4).

Race.—Thirty patients with a total of 39 admissions were Negroes, and 55 admissions in 48 patients occurred in Caucasians. Considering the ratio of Negro to white admissions to the wards of the Graduate Hospital, this does not represent a racial predisposition or increased incidence of acute pancreatitis among Negroes. Acute or chronic alcoholism was three times as frequent as biliary tract disease in Negroes. In Caucasians, biliary tract disease was encountered twice as frequently as alcoholism. Concomitant biliary tract disease was seen in only 12% of Negro males. Alcoholism was a factor in only 5% of white females (Table 5).

Previous Episodes.—In 21% of the admissions a history of proved prior episodes of pancreatitis was available either in previous records in our hospital or in other hospitals. Prior episodes of pancreatitis were more fre-

TABLE 5.—*Race*

	Negro				White			
	Admissions		Patients		Admissions		Patients	
	No.	%	No.	%	No.	%	No.	%
Biliary tract	6	15	6	20	33	60	30	63
Alcoholic	27	70	20	66	14	25	11	23
Miscellaneous	6	15	4	14	8	15	7	14
Total	39		30		55		48	

TABLE 6.—*Previous Episodes of Pain*

	Biliary Tract		Alcoholic		Miscellaneous		Total	
	Admissions	%	Admissions	%	Admissions	%	No.	%
None	8	22	11	27	4	29	23	24
Similar	28	71	18	44	6	42	52	55
Proved	3	7	12	29	4	29	19	21
Total	39		41		14		94	100

quent in the alcohol group (29%) than in the biliary tract disease group (7%). Pancreatitis recurred in two patients after cholecystostomy and in one after cholecystectomy. Many additional patients (55% of all admissions) gave a history of having had pain attacks previously, which were quite similar to the recent episode of acute pancreatitis. However, the antecedent pain attacks were often described as being of lesser intensity and of shorter duration. It is possible that many of these episodes, occurring in the biliary tract group, were merely attacks of biliary colic rather than episodes of acute pancreatitis (Table 6).

Pain.—Pain was a major symptom in 98% of patient admissions. In the other two patients, the acute episode of pancreatitis occurred immediately after an abdominal operation. In these patients it was not possible to evaluate the significance of pain, because of the usual postoperative discomfort. Furthermore, the patients were receiving meperidine (Demerol) and sedatives. The objective signs in the postoperative cases which alerted the physician to the possibility of a complication were fever, a fall in blood pressure, and abdominal distention. In 78% of patients with an adequate history the onset of pain was sudden, while in 22% it was of gradual onset. The character of the pain was constant, with little fluctuation of intensity, in 59%, and it was described as being colicky or somewhat intermittent in 41% of patients with pain.

The initial location, in the majority of instances, was in the epigastrium, but other locations were not unusual (Table 7). One-third of the patients with concomitant biliary tract disease described the initial pain as being in the right upper abdominal quadrant, whereas left upper abdominal pain was not unusual in the alcohol group. Some radiation of the initial pain was present in 78% of patients. The commonest site of radiation was to the back (Table 8).

TABLE 7.—*Primary Site of Pain in Ninety-Two Attacks of Pancreatitis*

	Alcohol Group		Biliary Tract Group		Miscellaneous Group		Total	
	No.	%	No.	%	No.	%	No.	%
None	0	..	0	..	2	14	2	..
Epigastric	23	56	21	54	6	43	50	53
Upper abdominal	3	..	1	..	0	..	4	..
RUQ	3	..	14	35	2	14	19	20
LUQ	4	10	2	..	3	21	9	10
Lower abdominal	4	10	0	..	1	..	5	..
LLQ	4	10	1	..	0	..	5	..
Total	41		39		14		94	

TABLE 8.—*Distribution of Pain Experienced as Radiation from Initial Site*

	Alcohol Group		Biliary Tract Group		Miscellaneous Group		Total	
	No.	%	No.	%	No.	%	No.	%
None	8	20	10	25	5	42	23	25
Upper abdominal	4	10	6	16	0	..	10	11
RUQ	1	..	4	10	0	..	5	..
LUQ	2	..	0	..	0	..	2	..
Lower abdominal	3	..	1	..	0	..	4	..
RLQ	1	..	0	..	0	..	1	..
LLQ	2	..	0	..	0	..	2	..
Back	20	49	18	46	5	42	43	48
Diffuse abdominal pain	0	..	0	..	2	16	2	27
Total	41		39		12		92	

PHYSICAL EXAMINATION

Temperature.—The median temperature of all admissions was 100.5 F, although in 20% of patients the temperature was normal. Temperatures above 102 F were relatively infrequent.

Shock.—Signs and symptoms of shock were present in six patients. Only those patients who presented unequivocal manifestations, including a low systolic and diastolic pressure, were considered to be in shock. A persistent lowering of the blood pressure to shock levels was a bad prognostic sign, being followed by death in two instances. One patient with biliary tract disease and chronic alcoholism was first seen three weeks

after the onset of pain. He was moribund and died about 30 hours after admission. Necropsy showed a diffuse hemorrhagic pancreatitis. In two additional instances, a persistent fall in blood pressure in the immediate postoperative period was the major sign of acute pancreatitis. In one of these, necropsy also showed diffuse hemorrhagic pancreatitis. The remaining three patients with manifest shock were in the alcohol group.

Icterus.—Visible icterus was seen in 20 patients of the group with biliary tract disease and in 1 patient of the alcohol group (this latter patient had a serum bilirubin level of only 1.5 mg. per 100 cc.).

Chest Findings.—Abnormal physical findings in the lungs were described in 30% of the admissions. The commonest finding was the presence of rales. In a few instances rhonchi or tubular breath sounds were heard or there were no breath sounds. One patient had a definite friction rub in the right base posteriorly. In the alcohol group these signs were predominantly on the left side, while in the biliary tract disease group the right chest was more frequently involved.

Abdominal Findings.—One or more abnormal physical findings were noted at the time of initial examination of the abdomen in 92% of patient admissions. The commonest finding was tenderness at the site of severest pain. Rebound tenderness and muscle guarding were less frequently encountered. Distention was present in 22% of the attacks. In the majority of patients, peristalsis was normal. In 16% of them it was decreased or absent, while in 6% the observers felt that peristalsis was increased. In some instances in which definite abdominal distention was recorded, peristalsis was thought to be normal. A mass was thought to be palpable in 12 patients (Table 9).

TABLE 9.—*Abdominal Findings in Ninety-Two Attacks of Acute Pancreatitis*

	Alcohol Group		Biliary Tract Group		Miscellaneous Group		Total	
	No.	%	No.	%	No.	%	No.	%
Direct tenderness	36	87	36	92	10	70	82	87
Rebound tenderness	8	19	11	28	2	14	21	22
Muscle guarding	14	34	16	41	6	42	32	34
Distention	9	22	6	15	6	42	21	22
Peristalsis								
Normal	28	68	26	67	9	64	63	68
Absent	2	5	3	8	1	7	6	6
Increased	4	10	2	5	0	..	6	6
Decreased	7	17	8	20	4	29	19	20
Masses								
RUQ	2	..	5	..	1	..	8	..
LUQ	2	..	2	..	0	..	4	..

Thrombophlebitis of the leg veins was seen in three patients. One of these probably had a pulmonary infarct. Another patient was thought to have multiple small pulmonary infarcts.

LABORATORY FINDINGS

Leucocyte Count.—The white cell counts ranged from 5,000 to 30,000 cells per cubic millimeter. It is of interest that in 60% of patients in the alcohol group the leucocyte count was 10,000 cells per cubic millimeter or less. In acute pancreatitis due to other causes, the range of leucocyte counts was fairly evenly distributed between 5,000 and 20,000 cells per cubic millimeter.

Serum Bilirubin Concentration.—These values were available in 82% of cases. In the alcohol group 75% of the values were 1 mg. per 100 cc. or less and the other 25% ranged from 1.0 to 1.5 mg. per 100 cc. None were above 1.5 mg. per 100 cc. The concentration of serum bilirubin in the biliary tract disease group ranged from 0.2 to 10 mg. per 100 cc. Thirty per cent had 1 mg. or less; in 15% the concentration was between 1.0 and 1.5 mg. per 100 cc., while the remaining 55% had levels between 1.5 and 10.0 mg. per 100 cc. A common-duct stone was present in two of these, and a thickened common duct without stones, in another.

Serum Alkaline Phosphatase Values.—These data were available for 43 patients. Increased concentrations were recorded in one patient in the alcohol group and in four patients in the biliary tract group. The patient in the alcohol group also had cirrhosis, but the serum bilirubin concentration was normal. The four patients in the biliary tract group with hyperphosphatasemia also had elevated bilirubin levels. Two patients had cholecystolithiasis; one had a common-duct stone, and the common duct was found thick-

ened but without a stone present at the time of exploration in the remaining patient.

Liver-Function Tests.—Adequate studies of liver function were available in 64% of cases. Liver function was considered impaired if one or more of the following were present: positive cephalin-cholesterol flocculation and thymol-turbidity tests, persistent sulfobromophthalein (Bromosulfalein) retention, reversal of the A/G ratio, or persistently low prothrombin concentrations. Excessive sulfobromophthalein retention subsiding within two weeks of admission was not considered indicative of chronic liver damage. In 14 cases an abnormal retention was seen early after the acute attack, and normal clearance

TABLE 10.—*Serum Bilirubin Values in Patients with Abnormal Retention of Sulfobromophthalein in Whom Clearance Subsequently Became Normal*

	Cases, No.
I. Biliary tract disease	
Serum bilirubin >3.0 mg.	3
Serum bilirubin ≦1.5 mg.	3
II. Alcohol	
Serum bilirubin ≦1.0 mg.	7
Serum bilirubin 1.5 mg.	1

of sulfobromophthalein was obtained when the test was repeated later. This phenomenon was observed in a number of patients who were not jaundiced (Table 10). It may be that the mechanism responsible for sulfobromophthalein retention soon after the acute attack may account for some instances of nonvisualization of the gall bladder with oral dye which has been noted to occur at times shortly after an episode of acute pancreatitis.

If we use the above criteria for liver damage and exclude those cases with transient sulfobromophthalein retention, 20% of the alcohol group and 4% of the biliary tract group had evidence of impaired liver function.

Serum Calcium Concentrations.—These determinations were available in 64 admissions. Normal values (9 to 11 mg. per 100 cc.) on one or more determinations were found in 50 cases. However, only 16 of these had adequate serial serum studies. There were 14 patients who had low serum calcium

TABLE 11.—*Calcium Determinations in Sixty-Four Patients*

	Patients, No.
Normal values	
(a) Only 1 determination before 3d day or after 7th	34
(b) Serial determinations	16
	50
Abnormal values	
7.0-8.0 mg.	5*
8.0-9.0 mg.	9
	14
Correlation of pathology with low serum calcium	
(a) No pathology available	8
(b) Necrosis	4
(c) Edema (calcium 8.2 and 8.8 mg.)	2

* 1 patient had tetany. Serum calcium was 7.2 mg. per 100 cc.

levels (Table 11). One patient with a serum calcium of 7.2 mg. per 100 cc. had tetany. A pathologic diagnosis was available in six cases with hypocalcemia. Four had necrotizing pancreatitis, and two supposedly had pancreatic edema.

Blood Glucose Determinations.—Disturbance in glucose metabolism was seen in 25 patients, 1 of whom had diabetes prior to the onset of pancreatitis. The commonest disturbance was a mild transient hyperglycemia (Table 12). It is likely that at least four patients developed permanent diabetes.

Serum Amylase.—Serum amylase determinations were available in 93% of cases. This determination was done on admission in the overwhelming majority of patients. However, in a few instances it was not determined until 48 hours after admission, and in four cases enzyme determinations were not obtained until after an exploratory laparotomy. Usually the initial serum amylase showed the maximum elevation; however, in certain instances the amylase values fluctuated markedly and the maximum elevation occurred at a later time.

TABLE 12.—*Disturbance of Glucose Metabolism*

	Patients, No.
1. Normal blood glucose*	57
2. Diabetes prior to attack	1
3. Transient hyperglycemia	17
4. Diabetes†	4
5. Diabetic glucose tolerance	3

* 1 or more determinations.
† Hyperglycemia persistent two weeks or more.

A normal serum amylase was persistently present in 11% of patients. Most of these were admitted several days after the onset of symptoms. Since the amylase concentration tends to return to normal fairly rapidly after the initial elevation, the determination may have been done too late to pick up the elevation. Nine of the patients with normal amylase values had an increased concentration of lipase. In two patients, however, who subsequently went to necropsy, both the serum amylase and lipase were normal shortly before death. In both patients, a severe hemorrhagic pancreatitis was the cause of death.

In 42% of cases, the serum amylase elevation was less than five times our average top normal values (500 mg. per 100 cc. or less), while in 47% the concentration of amylase was more than five times the high normal figure. This breakdown is given because we have found that concentrations of amylase above five times top normal values almost always indicate a diagnosis of acute primary pancreatitis (excluding parotitis, uremia, and prior opiate injection).* Increased amylase values falling below this range may be found in other acute abdominal conditions and in uremia.[6]

There was no close correlation between the severity of the clinical signs of toxicity and the serum amylase value. A number of patients who had a marked rise in temperature or striking leucocytosis showed a minimal elevation in serum amylase. However, all patients with a serum amylase elevation to 900 mg. per 100 cc. or higher did have a temperature of 101 F or higher and/or a white cell count of 15,000 or more.

Usually the serum amylase concentration returned to normal values within a few days after medical therapy was instituted. This occurred regardless of the height of the initial amylase elevation. High amylase values persisted longer in the alcohol group than in the biliary tract group. Twenty-four patients had hyperamylasemia for 10 days or longer after medical therapy was begun (Table 13).

TABLE 13.—*Analysis of Persistent Elevation of Serum Amylase and Lipase*

Case No.	Etiology	Maximum Amylase, Mg./100 Cc.	Maximum Lipase, Cc./100 Cc.	Duration of Elevation, Days
I. Recurrent acute pancreatitis				
23	Unknown	300	1.5	10
57	Alcohol	400	6.0	17*
59	Alcohol	800	10.0	20†
49	Alcohol	400	5.0	20
38	Alcohol	200	4.0	10†
34A	Alcohol	700	9.0	15†
72	Alcohol	300	3.0	10†
II. Pancreatic fibrosis or persistent edema				
53	Biliary tract disease	300	3.0	25†
42	Biliary tract disease	500	6.0	17
37	Biliary tract disease	2,200	16.0	14*
33	Biliary tract disease	300	4.0	10
III. Pancreatic cyst				
60	Biliary tract	1,100	7.0	14
63	Alcohol	700	...	30†
76	Alcohol	500	6.0	20*
78	Biliary tract	1,000	4.0	39*
IV. Pancreatic fistula				
40	After gastric resection	1,000	9.0	20†
V. Abscess				
34	Unknown	900	5.0	20*
VI. No known complications				
35	Unknown	1,200	9.0	20†
46	Alcohol	600	5.0	30†
2	Alcohol	400	4.0	15†
9	Alcohol	300	4.0	13†
17	Alcohol	500	4.0	17†
25	Alcohol	700	4.0	19
29	Biliary tract	1,100	6.0	10

* Surgery.
† Discharged.

No apparent cause for the persistence of the elevated amylase value could be found in 29% of patients. An equal number (29%) had had previous recurrent episodes of acute pancreatitis. Seventeen per cent of the group with prolonged hyperamylasemia had pancreatic fibrosis or persistent edema of the pancreas at laparotomy, and 17% had pseudocysts of the pancreas. Other causes of prolonged elevation of amylase values were pancreatic fistula (one case) and a pancreatic abscess (one case). Thus, in 71% of cases with a persistent elevation of serum amylase a complication was proved.

Serum Lipase Values.—These determinations were available in 88% of cases. The lipase figures were normal in 13 patients (16%). Serum amylase values were elevated

* References 3-5.

in 11 of the patients whose lipase levels were normal. In 57% of those with lipase determinations, the lipase was less than five times the average top normal (5 cc. or less), while in 27% it was greater than five times top normal value. Thus, the serum lipase tended to be relatively lower than the amylase concentrations which were five times top normal or greater in 47% of cases. However, the serum lipase values did not show as much fluctuation as the serum amylase figures.

Electrocardiograms. — Electrocardiograms were available in 51 patients. Of these, 11 were interpreted as being normal; 36 had some evidence of myocardial abnormality and/or an electrolyte imbalance. In four patients an acute myocardial infarction could not be ruled out in the initial electrocardiogram. Serial tracings were subsequently normal in two of these patients, while one of them had a myocardial infarct and another patient very probably had a concomitant infarct. Abnormal electrocardiographic tracings suggestive of myocardial abnormalities have been reported previously many times.†

In previous publications we have discussed the difficulties in differential diagnosis due to electrocardiographic abnormalities.[8] It should be emphasized that the serum pancreatic enzyme tests provide greater assistance than electrocardiographic tracings in the differential diagnosis of myocardial infarction and acute pancreatitis.

X-RAY FEATURES

Survey Films of the Abdomen.—These were available in 50 admissions. Pneumoperitoneum was not encountered. On the original reports, pancreatitis was mentioned as a possibility in the differential diagnosis in only 14% (Table 14). For the purpose of this report, these films were reviewed again, and particular attention was given to the amount and distribution of air in the intestinal tract.

The following criteria were regarded as evidence of localized ileus secondary to peritoneal irritation: (1) the presence of air in a few small-bowel loops which were adjacent to each other and the absence of significant air in other small intestinal loops, (2) small amounts of air in either the stomach and/or colon (regarded as corroborative evidence), (3) caliber of the air-filled loops at least 2.5 to 3 cm., (4) a stiffened appearance of the gas-filled loops and the space between the adjacent loops wider than normal.

If the above signs of localized ileus were present in the upper abdomen, either in the midline or left side, pancreatitis was suggested. Changes in the duodenum, when present, added further confirmation. Localized ileus must be distinguished from aerophagia. In the latter, the air is distributed uniformly throughout the entire gastrointestinal tract or it is scattered in the stomach, multiple small-bowel loops, and several portions of the colon. The small-bowel loops are not dilated.

In reviewing the abdominal films of the cases of pancreatitis, 22 normal films were added. The roentgenologist (G. S.) read the complete series without knowing the names or histories. In only 2 of the 22 normal films (9%) did he feel that pancreatitis was suggested (Table 14). Twenty-three of the abdominal films of the cases of pancreatitis were interpreted as being normal, while twenty-three showed localized ileus suggestive of pancreatitis, and in four mechanical obstruc-

TABLE 14.—*Evaluation of Abdominal Flat Films*

A. Original diagnosis			Cases No.
Normal			35
Pancreatitis (possible)			7
Mechanical obstruction or ileus			8
Total			50
B. Review diagnoses			
Normal			23
Consistent with pancreatitis			23
Mechanical obstruction or ileus or pancreatitis			4
Total			50
C. Abnormal films	Pos.	Neg.	Total
Biliary tract group	7	15	22
Alcohol group	16	6	22
Miscellaneous group	4	2	6
Total	27	23	50
D. Comparison with flat films of normal persons			
Normals	2	20	22
Pancreatitis	27	23	50

† References 7-9.

TABLE 15.—*Chest X-Rays (Thirty Cases)*

	Cases, No.
A. General findings	
Within normal limits	14
Bilateral abnormalities	4
Right side abnormalities	9
Left side abnormalities	3
B. Specific findings	
Elevation of diaphragm	7
Pneumonitis or atelectasis	9
Fluid	2

tion or generalized ileus was suggested. It is of some interest that positive findings were more frequent in the alcohol than in the biliary tract group of patients.

Chest X-Rays.—Early films of the chest were available for review in 30 cases. Sixteen showed some pathology, including elevation of the diaphragm, pneumonitis, linear atelectasis, or hydrothorax (Table 15).

Barium-Meal Studies.—Barium studies of the stomach and duodenum performed between 6 and 31 days after the acute attack were available in 29 cases. Coarsening of the gastric and duodenal mucosa was common. There was some suggestion of a mass in 14 cases. The signs suggesting a mass included extrinsic pressure on the stomach, extrinsic pressure or widening of the duodenal loop, and/or displacement of the duodenojejunal angle.‡ There were five patients in whom the small bowel was studied. All showed some disturbance of motor physiology. In four studies hypermotility was present (Table 16).

Cholecystograms.—In all instances of pancreatitis subsequently proved to be associated with biliary tract disease, the cholecystograms, when available, were abnormal. In the alcohol group, 12 of the 14 cholecystographic studies, obtained between 4 and 14 days after the acute attack, were normal. In two there was "nonvisualization." However, in one of these a later cholecystogram (21 days) showed normal function. Accumulation of viscid bile in the gall bladder, which does not mix readily with dye-containing hepatic bile, may account for nonvisualization when vigorous gall-bladder evacuation has not occurred for a number of days while patients are on the fat-free regimen employed in the management of the pancreatitis. All of the cholecystograms obtained two weeks or more after the acute attack were normal in the alcoholic group.

TABLE 17.—*Cholecystograms*

	Patients, No.
I. Biliary tract group (36)	
A. Patients operated on	
1. Cholecystogram not obtained	10
2. Cholelithiasis	9
3. Nonvisualization	4
B. Patients not operated on	
1. Cholelithiasis	8
2. Nonvisualization	5
II. Alcohol group (31)	
1. Cholecystogram not obtained	10
2. Normal cholecystogram	19
3. Dilated C. D.; normal G. B.	1
4. Question of stones vs. gas shadow	1

Pancreatic Lithiasis.—There were seven instances of pancreatic lithiasis. Six of these were in the alcohol group, and one was in the biliary tract group.

CLINICOPATHOLOGIC CORRELATION

Necrosis vs. Edema.—A pathologic diagnosis was established in 27 patients. This was accomplished at laparotomy in 11 patients during the acute phase of the disease and at necropsy in 3. The remaining patients had elective biliary tract operations from one to five weeks after admission. Necrotizing pancreatitis was somewhat more frequent in

‡ Bove, P.: Treatment of Acute Pancreatitis, read before the Inter-American Association of Gastroenterology, Mexico, D. F., May 14, 1952; Cintra do Prado, F.: Clinical Aspects of Pancreatitis, read before the Inter-American Association of Gastroenterology, Mexico, D. F., May 14, 1952; Santos, F.: Personal communication to the authors.

TABLE 16.—*Barium-Meal Studies Between Six and Thirty Days After Acute Attack* (Twenty-Nine Cases)*

Change	Present	Absent
Coarsening of gastric mucosa	10	19
Coarsening of duodenal mucosa	8	21
Evidence of a mass	14	15
(a) Extrinsic pressure on stomach	11	18
(b) Widening or pressure on loop	7	22
(c) Displacement of muscle of Treitz	4	25

* Average interval was about 18 days.

the alcohol group than in the biliary tract disease group. There was no apparent sex difference. Analysis of the initial temperature, leucocyte count, most physical findings, and enzyme levels disclosed very little difference between the two groups. Certain findings, however, were more frequent in those with necrotizing lesions, although the number of proved cases is too small to allow definitive conclusions. Shock was seen only in those patients with necrosis, and 3 of 14 patients with necrosis had this sign. Thromboembolic phenomena and significant skin changes (patchy cyanosis) were seen only in cases with necrosis. Decreased serum calcium concentrations were more frequent in the patients with necrotizing pancreatitis, and values below 8.0 mg. per 100 cc. were seen only in the necrosis group. The average duration of hyperenzymemia was greater in necrosis than in edema. Complications such as collection of fluid, abscesses, and fistulae were seen only in patients with necrosis. The four patients who died all had hemorrhagic pancreatitis (Table 18).

TABLE 18.—*Clinical-Pathologic Correlation in Twenty-Seven Cases**

	Edema	Necrosis
Etiology		
Biliary tract	11	7
Alcohol	2	5
Other	0	2
Male	7	8
Female	6	6
Temperature, F		
≦102	12	12
>102	1	2
White cell count		
≦15,000	9	7
>15,000	4	7
Abdominal signs		
Tenderness (direct)	13	12
Tenderness (rebound)	4	4
Rigidity	4	5
Distention	1	4
Normal peristalsis	7	4
Increased peristalsis	2	1
Decreased peristalsis	2	4
Absent peristalsis	2	4
Shock	0	3
Amylase		
≦500 mg./100 cc.	6	7
>500 mg./100 cc.	5	4
Not done	2	3
Lipase		
≦5 cc.	5	5
>5 cc.	6	3
Not done	2	6
Low serum calcium	2	4
Thromboembolic phenomena	0	2
Skin changes	0	2
Complications	0	5
Average duration of hyperenzymemia, days	9.6	13.6
Mortality	0	4

* Nature of pathology proved by operation or necropsy.

THERAPY

Twelve cases were explored within 48 hours of admission. In none of these patients was pancreatitis diagnosed prior to surgery. The preoperative diagnoses included cholecystitis in five instances, ruptured viscus in four, and, in one patient each, ectopic pregnancy, ruptured tubo-ovarian abscess, and acute appendicitis. Serum amylase determinations were available preoperatively in only three patients. In one it was normal. The second had an amylase of 250 mg. per 100 cc., and it was felt by the clinician that this was not diagnostic of acute pancreatitis but the result of some other abdominal inflammatory condition. The differential diagnosis of the third patient was very difficult. He had been hospitalized previously, and a persistent, asymptomatic serum amylase value of 800 to 1200 mg. per 100 cc. was present. Several weeks after discharge he was readmitted with acute abdominal pain and the amylase was 600 mg. per 100 cc. The surgeon decided to explore. Acute hemorrhagic pancreatitis with serosanguinous collection was found.

Ten patients had a very stormy postoperative course with a prolonged convalescence, and three died in the postoperative period. Thus, the mortality was 25%. This relatively high mortality was probably due to several factors. First, these patients were on the average more severely ill than many of the other patients. Second, several were chronic alcoholics and thus poorer surgical risks. Third, manipulation of an inflamed pancreas during the surgical procedure may have accentuated the inflammatory process. Finally, adrenal insufficiency (stress) may also have been a factor. At necropsy one patient did have adrenal cortex atrophy. It is of interest that in one of the two patients that did not have a complicated postoperative course only local anesthesia was used during surgical exploration. All of the patients who had elective delayed surgery had an uncompli-

cated postoperative course, and among them there were no deaths as a result of surgery.

There was one death among the 82 patients treated medically during the acute stage of their disease. This represents a mortality of 1.3%. The patient who died was a chronic alcoholic who was admitted three weeks after the onset of symptoms. On admission he was in a semimoribund state, with shock, marked dyspnea, and abdominal distention. He died 36 hours after admission. Positive findings at autopsy were acute hemorrhagic pancreatitis and cholelithiasis (Table 19). The over-all mortality in the entire group was 4%. The objectives and rationale of the nonoperative conservative regimen have been presented in detail elsewhere.§

TABLE 19.—*Therapy*

	Cases, No.	Postoperative Course: Normal No.	Normal %	Stormy No.	Stormy %	Mortality No.	Mortality %
Immediate surgery..	12	2	16	10	84	3	25
Elective surgery.....	19	19	100	0	..	0	..
Medical therapy (acute phase).....	82	..	..	..	..	1	1.3

COMMENT

Mention has been made of the ability to obtain a history of excessive imbibance of alcohol or of the presence of biliary tract disease in patients with acute pancreatitis.‖ In the present larger series of cases we have once more noted the etiologic importance of these two factors. It is likely that overindulgence in alcohol or biliary tract disease played a significant role pathogenetically in at least 86% of these patients. The cases have been segregated into these two major groups, "pancreatitis-alcohol" (P-A) and "pancreatitis-biliary" (P-B) in order to determine whether any significant differences (clinical, pathologic, prognostic) exist.

It will be noted that in "pancreatitis-alcohol" (41 admissions) the age of occurrence is younger and the male sex and Negro race predominate. Prior episodes of pancreatitis were commoner. Proved recurrences were four times more frequent in P-A as compared with P-B. Liver-function tests were often abnormal (20% in P-A; 4% in P-B). High serum amylase values persisted longer in P-A than in P-B cases. Likewise, roentgen findings suggestive of "pancreatic ileus" were encountered more often in P-A cases. Pancreatic calcinosis was noted in six P-A patients but in only one P-B patient.

In "pancreatitis-biliary" icterus commonly accompanied the attack, whereas in "pancreatitis-alcohol" it was noted only once. Hyperbilirubinemia (above 1.5 mg. per 100 cc.) was noted in 55% of cases in P-B and not once in P-A. Therefore, the association of significant hyperbilirubinemia with acute pancreatitis should suggest (as a rule) the existence of concomitant disease in the biliary tract. Fisher and McCloy, however, recorded the presence of jaundice in 7 and severe hepatic histologic changes in 11 of 14 fatal instances of acute hemorrhagic pancreatitis not associated with extrahepatic biliary tract disease.[13]

It appears that acute pancreatitis of alcoholic etiology is a severer disease, with a greater incidence of complications and recurrences and generally with a poorer prognosis. Although this review does not include a long-range follow-up, our patients in the P-B group who submitted to elective biliary tract surgery after subsidence of the acute attack seem to have a much lower incidence of recurrence of pancreatitis. In our experience relapsing pancreatitis in most instances has been encountered in the P-A group of patients.

Since the advent of the pancreatic serum enzyme tests, an increased incidence of acute pancreatitis in association with both acute cholecystitis and biliary colic has been noted. We believe that immediate operation is contraindicated in the presence of acute pancreatitis, unless clear-cut indications render operation imperative. For some years, serum enzyme tests have been employed in all patients admitted to our service who have symptoms and signs suggesting acute cholecystitis or biliary colic. If this policy is not adopted, one certainly should do serum enzyme tests

§ References 1 and 10.

‖ References 1, 11, and 12.

when an increased likelihood of acute pancreatitis is suggested by (1) pain of greater intensity than is anticipated in attacks of "pure biliary colic," particularly if its greatest intensity remains in the epigastrium or radiates to the left upper abdomen or to the region of the angle of the left scapula; (2) association of shock-like state; (3) striking constitutional reaction, greater elevation in temperature, and higher leucocytosis, and (4) failure to obtain lasting relief from opitate injection. If hyperenzymemia is noted, our policy is to delay operation for the biliary tract disease until the pancreas has had time to "cool off," as indicated by a return to normal of the enzyme values. Hyperbilirubinemia is often concomitantly present in such instances and ofttimes the concentration of serum bilirubin will return to normal concomitantly. If this fortunate happenstance does take place, the patient is a better operative risk and definitive surgery is more easily accomplished. Obviously, the acuity of the biliary lesion demands earlier operation in some instances. Acute pancreatitis may develop later during the course of observation in patients with acute biliary tract disease, when it has not been noted on admission. In patients with acute biliary tract disease, hyperenzymemia may be absent on admission to the hospital but may develop some days later, during the period of observation. The possibility of the development of acute pancreatitis should ever be in mind in the case of those patients whose convalescence from an "acute biliary attack" is not satisfactory. Enzyme determinations should be frequently repeated under these circumstances.

SUMMARY

The clinical manifestations in 94 admissions of 78 patients with acute pancreatitis at the Graduate Hospital are reviewed.

Eighty-five per cent of the cases were associated definitely with either excessive imbibition of alcohol or biliary tract disease. These are unquestionably the commonest factors related to the etiology of acute pancreatitis. Other causes included operative trauma, allergy, and carcinoma of the pancreas.

The age of these patients ranged from 19 to 87 years. The mean age at the onset of the disease was younger in the alcohol group than in the biliary tract group. Alcohol was the major precipitating cause in Negroes, whereas associated biliary tract disease was noted more frequently in white patients. Proved recurrences of pancreatitis were four times more frequent in the alcohol group than in the biliary tract group.

Pain was the major symptom in 98% of patients. The common location of initial pain was in the epigastrium with radiation to the back. Other locations were not infrequent. Nausea and vomiting were present in the majority of patients.

On physical examination the commonest finding was direct abdominal tenderness. Muscle guarding, rebound tenderness, and distention were less frequent. Peristalsis varied from hyperactive to absent. Unequivocal signs of shock were seen in only 6% of patients. Visible icterus occurred in 52% of those patients who had associated biliary tract disease.

The most valuable diagnostic tools were the serum amylase and lipase tests. In those cases in which one or both enzyme studies were available (92 cases) either the amylase or lipase value or both were elevated in all but two instances. The latter patients had severe hemorrhagic necrosis. The serum amylase was 500 mg. per 100 cc. or more in 47% of cases, while the lipase was 5.0 cc. or more in 28%. A persistent elevation of serum amylase after 10 days of adequate therapy usually indicated a complication such as pseudocyst, abscess, fibrosis, or persistent edema of the pancreas.

In this series of patients increased serum bilirubin concentration during the attack of pancreatitis indicated associated biliary tract disease. Certainly this cannot be true universally in patients with a severer acute necrosis. Nevertheless, it seems likely that definite hyperbilirubinemia occurring during the episode of acute pancreatitis usually means associated biliary tract disease, particularly calculous disease.

Survey films of the abdomen, when available, disclosed findings suggestive of localized paralytic ileus, which might be interpreted as pointing toward pancreatitis, in 23 of 50 cases. Findings of this nature can be looked upon as being suggestive but never pathognomonic of acute pancreatitis. In four instances the x-ray configuration was more suggestive of mechanical obstruction or of diffuse paralytic ileus.

X-rays of the chest were abnormal in 16 of 30 patients. The changes included pneumonitis, linear atelectasis, and elevation of one or both diaphragms.

Barium-meal studies of the stomach and duodenum in 29 patients, carried out from 6 to 30 days after the attack, disclosed coarsening of the gastric and duodenal mucosa in many instances. Defects suggesting the likelihood of a mass in the region of the pancreas were seen in 14 of 29 cases.

In the clinicopathologic correlation, utilizing only pathologically proved cases (27 cases), the clinical and laboratory features of cases with edema are compared with those of acute necrotizing pancreatitis. It may be impossible to distinguish between necrosis and edema early in the course of the attack. However, in many instances of severe necrosis the occurrence of shock, hypocalcemia, prolonged hyperenzymemia, skin changes, thromboembolic phenomena, and complications are highly suggestive of the severer form of the disease.

In 43% of patients the admission diagnosis was incorrect. These incorrect diagnoses included acute cholecystitis, cholelithiasis, intestinal obstruction, ectopic pregnancy, ruptured viscus, acute appendicitis, and acute gastroenteritis.

The total mortality was 4.3%. There were 14 cases of necrotizing pancreatitis proved at surgery or necropsy. Eight of these had laparotomy during the acute phase, and three died (37.5%). Five were treated medically during the acute phase and survived subsequent surgery. One patient was admitted in a terminal state. All of the fatal cases were instances of necrotizing pancreatitis. The mortality among all patients in whom an exploratory laparotomy was performed within 72 hours of the acute attack was 25%, whereas there were no deaths of patients who had elective surgery after the acute symptoms subsided. There was 1 death among 82 patients treated medically during the acute phase of the disease.

CONCLUSIONS

The major etiologic factors in this series of cases of acute pancreatitis were overindulgence in alcohol and biliary tract disease. Certain differences in the clinical and laboratory findings in these two etiologic categories of patients are noted.

Serum amylase and lipase determinations are the most helpful laboratory aids to the diagnosis of acute pancreatitis, which may be varied and bizarre in its clinical masquerades.

Initially it is often impossible to distinguish between acute edema and acute necrosis of the pancreas. A critical analysis of the clinical features of these two groups of cases is given.

Prolonged elevation, with or without fluctuation, of the serum pancreatic enzymes while the patient is maintained on an adequate "pancreatic rest" medical regimen is usually due to a complication (abscess, pseudocyst, etc.).

A localized paralytic ileus involving one or more adjacent small-bowel loops in the left upper abdomen or midabdomen is suggestive but not pathognomonic of acute pancreatitis in the survey film of the abdomen.

This survey confirms our previous impression that the acute phase of pancreatitis is best treated by a nonoperative conservative regimen, provided other acute abdominal surgical emergencies can be excluded.

ABSTRACT OF DISCUSSION

DR. JAMES T. PRIESTLEY, Rochester, Minn.: This most enlightening study presented by Dr. Bockus has been of interest, I am sure, to us all. His critical appraisal of the etiologic factors and clinical manifestations of acute pancreatitis are thought-provoking and add significantly to our understanding of this serious disease. Of course not all of the questions are answered yet. One might ask why only a small proportion of patients who are chronic alcoholics or who have disease in

the biliary tract develop pancreatitis whereas the majority of these patients do not. The frequent association of pancreatitis and cholelithiasis without choledocholithiasis naturally suggests some etiologic relationship between these two conditions. Yet what is the exact mechanism involved? Might it even be possible in some cases that pancreatitis precedes the cholecystic disease? What proportion of patients who have an initial attack of pancreatitis will have subsequent attacks and perhaps develop the chronic relapsing form of this disease? There are of course many other unanswered questions, and studies such as those presented by Dr. Bockus will help answer some of these questions. We would hope that when more complete and specific knowledge of etiology is available that treatment would be more effective and perhaps prevention would be possible in some cases.

A word about treatment. Medical management is commonly accepted as the treatment of choice for acute pancreatitis, and the presentation which we have just heard adds further support to this opinion. Yet I believe we would all admit that it is not as satisfactory as we would like. For example, it is not always successful in preventing the development or progression of an acute pancreatic necrosis.

A common etiologic concept which is held regarding this form of the disease is that of continuing secretion of the pancreas in the presence of some degree of obstruction to the free and normal drainage of pancreatic juice, with resultant extravasation of pancreatic secretion from small radicals of the ductal system into the parenchyma of the gland. Perhaps bile may also be present in the pancreatic ducts under these circumstances, but I do not recall actually seeing bile-colored secretion in the pancreas in cases of this type. In any event, such a concept has some features in common with the production of acute pyelonephritis in the presence of ureteral obstruction or with production of cholangitis in the presence of choledochal obstruction. Recognized treatment of these conditions includes relief from the obstruction. One naturally wonders whether early relief from obstruction of the collecting system of the pancreas might not abort a process which otherwise, in at least some patients, progresses to a serious state and causes a prolonged illness. I realize that the mere suggestion of early surgical treatment of acute pancreatitis would meet with rather strenuous objection in many quarters, but perhaps the idea should not be entirely discarded.

My personal experience with pancreatitis has been largely with the chronic relapsing form of the disease. Recently, Taylor, Rogers, and I studied a group of patients to determine the late results following surgical treatment for chronic relapsing pancreatitis. A recent review of the clinical records of these patients as regards the incidence of alcoholism and biliary tract disease reveals findings similar in some regards but a little at variance in other regards with those presented by Dr. Bockus. There was a history of alcoholic intake of varying degree in 40% of our group of patients. Disease in the biliary tract was found in 72%, but in only 12% were there stones in the common duct. Twenty per cent had a history of both biliary tract disease and alcoholism.

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Useful Diagnostic Laboratory Procedures in Pancreatitis

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The purpose of this paper is to discuss some of the laboratory procedures which may be helpful in the diagnosis of pancreatitis. They include the determination of the degree of enzyme activity in blood serum, duodenal juice, urine, and peritoneal fluid; the microscopic examination and chemical analysis of stools for evidence of impaired fat and protein digestion, and the glucose-tolerance test. In addition, reference is made to other laboratory tests which may reveal abnormalities in pancreatitis, such as the serum calcium concentration, the differential white blood cell count, the various liver tests, and the starch-tolerance test.

A. ENZYMES IN BLOOD

Procedures are available for determining the amylase and lipase activity of serum; however, no direct method of estimating trypsin is as yet available. The plasma antithrombin titer, which Innerfield and co-workers [1] believe reflects tryptic activity, is being evaluated in pancreatic as well as other diseases.

1. *Serum Amylase.*—Of the four methods which have been used for estimating the amylolytic activity of serum, the saccharogenic,* the viscometric,† the starch-iodine,[6] and the nephelometric,[7] the saccharogenic (copper reduction) method of Somogyi is the most generally used and the most accurate; it requires about one hour for its performance. The range of values for normals commonly employed extends from 60 to 180 units (milligrams of glucose per 100 ml. of serum). The method involves the determination of the amount of glucose formed when starch is hydrolyzed by the amylase. A marked hyperglycemia may interfere with its accuracy.[8]

Recently, serum amylase tests have been modified so as to simplify the procedure and shorten the time required for their completion. Some of them have employed the starch-iodine method.‡ That reported by Fishman and Doubilet [10] can be performed in 10 minutes and requires a minimum of clinical apparatus. In the presence of high concentrations of amylase, all the starch present is digested; consequently a yellow color, instead of various shades of purple, is obtained when iodine is added. More recently, the turbidimetric method of Waldron [11] for measuring amylase activity of duodenal juice has been modified by Peralta and Reinhold [12] for estimating the amylase activity of serum. The basis of this method is the decrease in the absorbency of a buffered starch suspension caused by the splitting of the starch by the enzyme during a timed interval and at a controlled temperature. Such a method avoids the use of solutions of elemental iodine in laboratories in which microanalytical methods for iodine are employed and thus reduces the hazard of contamination to the latter.

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* References 2 and 3.

† References 4 and 5.

‡ References 9 and 10.

The serum amylase determination is the most generally useful procedure in the diagnosis of acute pancreatitis. Its concentration is increased to more than four to six times normal early in the attack and usually returns to normal within three to four days in uncomplicated cases. Persistent elevations (up to 22 days) indicate a continuation, extension, or progression of the process.[13] The height of the amylase level bears no constant relationship to the severity of the attack. The concentration may also be increased during the acute episodes of chronic relapsing pancreatitis, particularly early in the course of the disease. Subsequently, as the pancreas becomes progressively and extensively damaged, the functioning acinar cells may be too few to give an elevation during the acute flare-ups.

Increases in the serum amylase concentration have been reported in patients with carcinoma of the head of the pancreas,[14] in those in whom a peptic ulcer has penetrated into or near the pancreas,§ and when free perforation of an anterior duodenal ulcer has occurred into the peritoneal cavity. In the latter instance, the hyperamylasemia has been attributed to absorption of the enzyme from the peritoneal cavity. Elevated values have also been found when renal function is impaired [15] (paralleling the degree of azotemia), in peritonitis due to various causes,[17] in intestinal obstruction,‖ in mumps ¶ and other diseases of the salivary glands,[15] and following operations in or outside the abdomen.# They have been reported after thyroidectomy.* Increased, as well as normal and low, values have been reported in hepatic disease.[24] The elevations in serum amylase which have been noted in conditions other than acute pancreatitis were usually not as high (less than four to six times normal) as those encountered early in acute primary pancreatic inflammation.

§ References 15 and 16.

‖ References 16 and 17.

¶ References 15 and 18.

References 19-21.

* References 22 and 23.

Cause for confusion in the interpretation of the serum amylase value in acute pancreatitis has arisen as a result of the reported elevations in the sera of patients given opiates.† The problem raised by this possibility is important, because reliance cannot be placed on the test when a patient with abdominal pain presents himself for diagnosis after an opiate has been administered to him. The increases in serum amylase following a subcutaneous injection of 16 mg. of morphine sulfate in the three instances reported by Burke and co-workers [25] all occurred within the normal range of values (39 to 60, 20 to 56, and 24 to 80 units), the normal range in their laboratory being 6 to 99 units. Doses of codeine sulfate (2 grains [120 mg.]), larger than are ordinarily administered, have been reported to give rise to significant elevations in serum amylase and lipase in 6 of 27 cases.[27] An increased amylase level has been reported following an unstated amount of meperidine (Demerol) in one patient.[28] More recently, elevations in serum amylase following a subcutaneous injection of ¼ grain (15 mg.) of morphine sulfate have been reported by Bogoch and co-workers.[29] These workers noted an elevation in serum amylase in 3 out of 41 patients in the range of five times top-normal value (120 mg. per 100 cc.) in their laboratory. Increases above preinjection values were observed in eight other patients; however, the levels for these were not as high as might be expected to occur during the first 24 hours of an attack of acute pancreatitis. The increases were noted within 5 hours of the injection of morphine; however, in a few instances levels were still above top-normal 24 hours afterwards. Wapshaw [30] reported an increase in serum amylase and lipase levels in 5 (18%) of a group of 28 fasting patients given 0.016 gm. of morphine; the highest amylase level was 3 times, and highest lipase level, 20 times the premorphine level. In a second group of 28 patients, a meal was ingested 60 minutes prior to the morphine. Nine patients showed an increase in the serum amylase and lipase values. The

† References 25-27.

highest lipase level was 9 times, and the highest serum amylase level, 14.7 times the premedication level.

2. *Serum Lipase.*—The lipase activity of serum is determined by titrating with a standard solution of sodium hydroxide the fatty acid liberated as a result of hydrolysis of a neutral fat substrate (olive oil emulsion) by the lipase. The test, when olive oil is used as a substrate, as in the Cherry and Crandall [31] method, requires about 24 hours for its performance. Since decisions concerning management must often be made promptly in patients with acute abdominal pain, the 24-hour period required for the completion of the test mitigates against its usefulness in the diagnosis of acute pancreatitis. Values above 1.0 ml. N/20 NaOH are considered to be of significance by some,‡ and those above 1.5 cc. N/20 NaOH, by others.§ More recently, a titrimetric method has been described by Alper.[35] This employs a tributyrin substrate and requires one hour's incubation. Units of lipase activity are expressed as milliliters of N/10 NaOH required to neutralize the fatty acids produced by the action of lipase on the tributyrin substrate.

The serum lipase activity is increased early in an attack of acute pancreatitis and may remain elevated after the serum amylase has returned to normal.‖ It may also be increased early in the course of carcinoma of the head of the pancreas when the lesion obstructs the pancreatic ducts, before the acinar cells are destroyed.[36] Elevated serum lipase values have been reported in some patients with cholelithiasis and jaundice,[36] hepatic tumor,[36] viral hepatitis,[24] hepatic cirrhosis,¶ intestinal obstruction # (also in experimental ileus [38]), peritonitis,[17] after morphine sulfate injections,* and after large doses of codeine sulfate.[27]

3. *Plasma Antithrombin Titer.*—Because blood contains antitryptase, a satisfactory method for estimating serum trypsin directly has not thus far been available. However, Innerfield and co-workers [1] have postulated that the plasma antithrombin titer reflects the blood trypsin content. They have found the antithrombin titer to be elevated in acute pancreatitis and in some cases of chronic relapsing pancreatitis but not in acute surgical abdomen due to other causes. The experiences of others with the test in acute pancreatitis has been varied. Dreiling and coworkers [39] found elevations in the titer in 6 out of 49 patients without clinical or laboratory evidence of pancreatic disease. The amylase levels were normal in each of the six. In their series of 11 patients with acute pancreatitis, they found elevated titers in 3 in whom serum amylase levels were normal and normal titers in 2 with elevated amylase levels. Both tests were normal in three and both were elevated in three others. Welch † and also Levy ‡ felt that the test was not specific for pancreatitis. The experience of Moseley and co-workers [40] was more encouraging. These workers believed that the antithrombin test helped establish the diagnosis of acute pancreatitis more definitely in 11 of 13 patients. They felt that it was helpful either as a supplementary test confirming the clinical impression and amylase findings or as an aid in instances where the serum amylase values were borderline and slightly elevated for some cause other than acute pancreatitis. In their opinion, best results from the test were obtained when it was performed early in the course of the illness, but they found that it continued to be positive for at least 36 to 48 hours in many patients. They emphasized that the test had many pitfalls and that, unless strict attention to detail was paid, results might not be reproducible. It is of interest that they observed no elevations in titer after morphine.

‡ References 17, 24, and 32.

§ References 33 and 34.

‖ References 32 and 34.

¶ References 24 and 36.

References 17, 36, and 37.

* References 29 and 30.

† Welch, G. E., in discussion of Moseley.[40]

‡ Levy, J. S., in discussion of Moseley.[40]

B. ENZYMES IN URINE

The determination of the concentration of amylase in the urine was used for many years for the diagnosis of acute pancreatitis. More recently it has been employed less often, because examination of the blood serum for amylase has been found to be of greater diagnostic value. The determination of urinary lipase [41] has not been widely used, while a satisfactory method for determining urinary trypsin is not available.

The methods for determining amylase activity in serum are applicable to urine, but larger quantities of urine are necessary, because it has less amylolytic activity than serum. The saccharogenic method, modified § to correct for the normal reducing qualities of urine, is the most satisfactory. It is less reliable when a marked glycosuria is present. Random specimens may be misleading because of a lack of relationship between the blood and urinary amylase.‖ The normal range of urinary amylase, according to Nothman,[44] using the Somogyi saccharogenic method,[2] varies from 80 to 350 units per 100 ml., and, according to Dozzi,¶ also using a saccharogenic method, from 264 to 953 mg. per 100 ml. of urine per 24 hours. Jacobsson and Hansen [51] have recently published a turbidination method for determining amylase in the urine, using dextrin as a substrate. The urinary amylase determination has been thought to be useful occasionally when acute pancreatitis or an acute episode of chronic relapsing pancreatitis is suspected, because the urinary amylase may remain elevated after the serum amylase has returned to normal.

C. ENZYMES IN DUODENAL JUICE

The determination of the bicarbonate and enzyme content of duodenal juice aspirated before and after the intravenous or subcutaneous injection of a suitable stimulant of the external secretion of the pancreas can supply helpful information concerning pancreatic disease. However, the procedure cannot be performed readily in the patient sick with acute pancreatitis. If performed after the acute attack subsides, it may reveal evidence of pancreatic dysfunction and therefore is useful only if serum amylase determinations were not performed during the attack. The test is more helpful in the diagnosis of chronic pancreatitis. It is time-consuming and requires an elaborate set-up. Gastric and duodenal juice are aspirated and collected separately by continuous suction with the use of either two single-lumen tubes tied together or a double-lumen gastroduodenal tube such as that of Agren and Lagerlof [45] or of Abbott and Rawson.[46] By the use of such an arrangement most of the gastric juice and the greater part of the duodenal content (bile and pancreatic juice) are withdrawn separately.

The procedure necessitates the proper placement of the tube tips. This is best accomplished under fluoroscopic guidance. The gastric tube is intended to prevent gastric juice and swallowed saliva from entering the duodenum. The duodenal tube tip should be at or near the ampulla of Vater. Basal secretion is collected for a period of 20 minutes, after which a suitable stimulant is injected and three to four successive 20-minute samples of duodenal content are aspirated. The substances used for stimulating pancreatic secretion include secretin (1 clinical unit per kilogram of body weight, intravenously),# methacholine (Mecholyl) bromide (15 mg. subcutaneously),[47] and bethanechol (Urecholine) chloride (10 mg. subcutaneously).[49] Secretin evokes a large volume of juice rich in bicarbonate but poor in enzymes (hormonal secretin), while either methacholine or bethanechol produces a scant flow of juice poor in bicarbonate but rich in enzymes (neural secretion). Modifications of the Somogyi method for serum amylase, of the Cherry-Crandall method for lipase, and of the Riggs and Stadie[50] procedure for peptic activity are applicable for duodenal enzyme determinations. A turbidimetric method for estimation of amylase activity has been pub-

§ References 42 and 43.

‖ References 8, 42, and 43.

¶ References 8 and 42.

References 47 and 48.

lished by Guth and co-workers.[52] Bicarbonate content may be determined by titrating 5 ml. of each specimen of duodenal juice with N/10 NaOH after acidification with 10 ml. of 0.1 N HCl.

Evidence of deficient pancreatic secretion may be found in patients in whom the function of a sufficient number of acinar cells is impaired or destroyed by inflammation, as in subsiding acute pancreatitis or in chronic pancreatitis.

D. CONCENTRATION OF AMYLASE IN PERITONEAL FLUID

The determination of the concentration of amylase in peritoneal fluid obtained by abdominal paracentesis * has been utilized in the diagnosis of acute pancreatitis. The technique involves the introduction of a 20-gauge needle through the midline of the abdomen just below the umbilicus. The concentration of amylase has been reported to be increased to 300 or more Somogyi units and may remain so for two to four days after the blood level has returned to normal. In addition, the appearance of the aspirated fluid has furnished some information as to the type of pancreatitis present, a yellow turbid fluid indicating the edematous type and a reddish-brown color indicating the hemorrhagic form. The presence of bile and hydrochloric acid helps to differentiate pancreatitis from perforated peptic ulcer.

E. ENZYMES IN FECES

Examination of the feces for enzymes is not used for the study of the external secretion of the pancreas in acute pancreatitis or in chronic pancreatitis in adults. In infants the gelatin film test may be helpful in detecting the presence or absence of trypsin when fibrocystic disease of the pancreas is suspected.[55] Great caution must be exercised in performing and interpreting the test, because proteolytic bacteria of the feces are capable of digesting the gelatin on the film. A procedure for decreasing the concentration of bacteria by dilution is available.[56]

F. MICROSCOPIC EXAMINATION AND CHEMICAL ANALYSIS OF FECES

Examination of the feces for undigested food may often supply evidence of an inadequacy of the external secretion of the pancreas in chronic pancreatitis. In marked pancreatic insufficiency, the stool is bulky; glistening; pale, owing to the presence of fat, fatty acids, and soaps; rancid; has the consistency of thick butter, and usually floats near the surface of the water in the toilet bowl. The passage of feces consisting of masses of fat resembling butter or cream (steatorrhea) on a diet containing considerable amounts of fat is highly suggestive of pancreatic disease.

1. *Microscopic Examination.* — Microscopic examination of the stools in pancreatic achylia usually reveals large quantities of fat in the neutral form. Neutral fat appears as yellowish flakes or droplets; fatty acids, as flakes or needle-like crystals, and soaps, as amorphous flakes or rounded masses as well as needle-like crystals. Sudan III when added to the stool stains neutral fat red and free fatty acid orange. Soaps (combined fatty acids) remain unstained unless the fatty acids are liberated by the addition of a drop of 30% acetic acid and heated to the boiling point over a flame. Varying amounts of fatty acids may be found in the stools of patients with pancreatic insufficiency, as a result of their formation from neutral fat in the colon [44] by bacteria.

The finding in the stools of large numbers of undigested muscle fibers with preserved longitudinal and transverse striations (creatorrhea) on a diet containing large amounts of chopped beef or ham given raw or lightly broiled indicates a deficient digestion of protein. Muscle fibers, however, can be broken down by the intestinal bacteria in the presence of pancreatic insufficiency; hence, creatorrhea may be missed if the fecal material remains in the colon for a long time.[44] The presence of starch granules (amylorrhea) in the stool is of little diagnostic importance.

* References 53 and 54.

Starch granules stain blue on contact with strong iodine solution U. S. P. (Lugol's solution).

2. *Chemical Analysis of Feces for Fat and Nitrogen.*—The determination of the fat and nitrogen content of feces on a fixed dietary intake of fat, protein, and carbohydrate can supply important information in chronic pancreatitis. Usually the Schmidt diet,[57] or a modification of it,[44] is ingested over a period of three days. A readily identifiable substance such as carmine or charcoal is used to "mark off the stools." The usual procedure is to administer the carmine (0.3 gm.) in a capsule with the first meal.† On the morning of the fourth day, charcoal (1 gm.) is ingested with a breakfast consisting of milk. The stools are collected after beginning the test diet. The first stool containing charcoal is rejected. The stools should be preserved in alcohol (0.8 cc. of 95% ethyl alcohol with each gram of stool) rather than frozen, because it has been claimed that refrigeration does not prevent the splitting of neutral fat.

The Schmidt diet contains 105 gm. of protein, 135 gm. of fat, and 180 gm. of carbohydrate. In normal persons up to 6% of the fat and up to 8% of the nitrogen ingested while on such a diet are excreted in the feces.[57] In complete obstruction of the pancreatic ducts, about 60% of the ingested fat and about 50% of the ingested nitrogen may be recovered from the feces. Most of this fat is in the form of neutral fat. In sprue the total amount of stool fat may also be greatly increased; however, the larger proportion of it consists of free and combined fatty acids rather than of neutral fat. An increased amount of fat in the stools can also occur in common duct obstruction and when intestinal transport is very rapid.

The fecal nitrogen content may be greatly increased (azotorrhea) in pancreatic insufficiency. It is usually within normal limits in common duct obstruction and in sprue, although Comfort and co-workers [58] have found that losses of nitrogen may be excessive. They believe that fecal values for fat and nitrogen do not distinguish between idiopathic and pancreatogenous steatorrhea and that fecal nitrogen values should not be used for differentiating the two. The investigators, however, based their belief on fecal values for total fat rather than on relative proportions of neutral and split fats. Evidence of a diminished hydrolysis of protein in the intestines of patients with chronic pancreatitis has been obtained by the finding of an increased fecal excretion of orally administered I^{131}-labeled protein.[59]

† References 44 and 57.

G. GLUCOSE TOLERANCE

Investigation of the carbohydrate metabolism can have considerable diagnostic value in chronic pancreatitis. The oral glucose-tolerance test may yield a diabetic curve in patients with steatorrhea of pancreatic origin but a flat curve in the active stage of sprue. Impairment of glucose utilization is detectable when sufficient islet-cell damage has occurred as a result of inflammation. Other evidences of deranged carbohydrate metabolism may include hyperglycemia and glycosuria. Low values for blood glucose as well as a tolerance curve indicative of increased utilization of glucose may be obtained in islet-cell tumors.

Recently, Althausen and Uyeyama [60] have reported their experience with the starch-tolerance test. They feed a lemon-extract-flavored gelatinous mass consisting of 100 gm. of soluble starch and 450 ml. of water. Venous blood specimens are taken before, and one-half, one, two, and three hours after the administration of the starch. To interpret the results properly it is necessary to obtain, in addition, a glucose-tolerance curve, following ingestion of 100 gm. of glucose. The maximal rise in blood sugar during the glucose- and the starch-tolerance tests is determined by subtracting the value for the fasting blood sugar of each curve from that of the peak of the respective curves. Then, the extent to which the maximal rise in blood sugar after glucose exceeds that after starch is calculated in percentages and compared with the normal range obtained from patients without

diseases of the pancreas. The values in the controls of Althausen and Uyeyama ranged from —54% to +51%, with a mean of +13.9 and a standard deviation of 28.2. They found the test to be normal in 12 of 14 patients with chronic pancreatitis.

H. SERUM CALCIUM

The serum calcium may be lowered in acute hemorrhagic pancreatitis. The depressed values are usually observed within the 3d to 14th day after the onset of symptoms,‡ most frequently on the 4th and 5th days. The lowering of serum calcium has been attributed [63] to the marked mobilization of calcium in and around the pancreas as a result of the formation of calcium soaps with fatty acids liberated when neutral fat is hydrolyzed by the lipase released into the peritoneal cavity.[65] Values as low as 5.1 mg. per 100 ml. have been recorded in the absence of tetany.[66] In general, the most seriously ill patients have the lowest serum calcium values, presumably because the amount of calcium withdrawn from the blood depends on the extent of fat necrosis, which, in turn, is influenced by the severity and duration of the disease.

I. MISCELLANEOUS

Other positive laboratory findings, especially in acute pancreatitis, may include an elevated value for serum bilirubin; hypoprothrombinemia; positive cephalin-flocculation, colloidal-red, thymol-turbidity, and thymol-flocculation tests; hyperlipemia,[67] ketonuria, and bilirubinuria. Hyperlipemia, in acute pancreatitis, along with a milky serum has been observed to exist for weeks and may be related to a deficiency of a fat-utilizing substance normally elaborated by the pancreas.§ A significant reduction in lymphocytes in the differential blood smear has been reported as occurring within 48 hours of the onset of an attack of acute pancreatitis.[69] In chronic pancreatitis, associated with steatorrhea, an impaired vitamin-A-tolerance curve may be obtained.

‡ References *32* and 61-65.

§ References 67 and 68.

SUMMARY

Various laboratory procedures which may be helpful in the diagnosis of pancreatitis are presented, and their application is discussed. They include determination of the degree of enzyme activity in the blood serum, duodenal juice, urine, and peritoneal fluid; microscopic examination and chemical analysis of feces for evidence of impaired fat and protein digestion, and glucose-tolerance, serum calcium concentration, and liver tests.

The serum amylase test is the most widely used procedure in the diagnosis of and in following the course of acute pancreatitis, as well as the acute episodes of chronic relapsing pancreatitis.

In the diagnosis of chronic pancreatitis, with or without calcification, the determination of the concentration of enzymes in aspirated duodenal juice before and after the administration of a suitable stimulant, the microscopic examination of stools for fat and meat fibers, the chemical analysis of feces for total and split fat and nitrogen, and the oral glucose-tolerance test are the most useful procedures.

ABSTRACT OF DISCUSSION

DR. VINCE MOSELEY, Charleston, S. C.: Dr. Machella, in his presentation, has given us an excellent review of the various laboratory procedures which are of value in the diagnosis of pancreatic disorders. His review has been thorough, and he has pointed out to us the specificity, variability, and sources of error which may arise to invalidate many of these tests. I can find no pertinent omissions in his very complete coverage of this subject.

I do, however, have two points which I should like to mention in connection with the serum amylase test and the plasma antithrombin test.

First, from personal experience, I have found that the amylase test is often disappointingly of borderline or only slightly elevated concentration at the time a patient with acute edematous or relapsing pancreatitis is first seen. Second, blood amylase values have been observed fairly often to be elevated to a significant or borderline concentration in various abdominal disease states other than pancreatitis.

A group of 18 patients with acute edematous or acute relapsing pancreatitis, all of whom were definitely proved cases, were personally seen in

the wards of the Roper Hospital. In only 50% of these patients was the amylase test found to be definitely positive at the time of, or subsequent to, the hospital admission of the patient. In contradistinction, in this same group of patients the plasma antithrombin test was found to be positive in 85% and negative in only 15%.

To illustrate the usefulness of the antithrombin test as an aid in the diagnosis of acute relapsing pancreatitis, a situation in which the amylase concentration usually falls off very rapidly in a matter of 20 to 36 hours, I would like to show two slides. The first shows the amylase concentration in four patients who were seen early in the course of this disorder and on whom the test was run repeatedly. In these cases it can be seen that the antithrombin test remained significantly positive for a longer period than did the amylase test, as has been our general experience in other similar patients.

The second slide illustrates this point in relation to six patients with acute relapsing pancreatitis whose initial and subsequent amylase tests were obtained at a time long enough after onset so that the serum amylase concentration was no longer significantly elevated but the antithrombin test was still positive.

In 34 patients in whom pancreatitis was strongly suspected initially but in whom other definite diagnoses were later established, and in whom it was believed that pancreatitis was excluded by subsequent findings, either at laparotomy or on the basis of x-ray or other findings giving adequate explanation for the symptoms on a basis other than pancreatitis, the antithrombin test was negative in all instances. Included in this group of 34 patients were those with hepatitis (3), cholecystitis (4), peptic ulcer (4), and abdominal malignant disease (12), disease states in which other observers have reported the finding of a positive antithrombin test. In 29%, or roughly one-third of this group, a borderline or rising amlyase titer was observed, and in 14% of this group the elevation was of a fourfold degree. Others have made similar observations, as pointed out by Dr. Machella, and data from a paper by Edmundson and coworkers (*Am. J. Med.* **12**:34 (Jan.) 1952) illustrates this point. [slide]

In carcinoma of the pancreas we have observed on two occasions the test to be positive early in the course of the disease. Later it became negative. In eight other patients with malignant disease it was negative.

The amount of trypsin necessary to produce a rise in antithrombin activity appears to be small. Inhalation of 250,000 units of Tryptar by means of an aerosol nebulizer will produce a positive test in 30 minutes. [slide]

In summary, as an adjunct to the amylase test, I have found the antithrombin test to be useful as a diagnostic aid. It has the additional value of staying positive for a longer period of time than the amylase test in acute edematous relapsing pancreatitis. I believe it has proved of value in patients with borderline serum amylase concentrations due to pancreatitis and also when the amylase rise is associated as a laboratory finding in disease states other than pancreatitis. Personal observations in 13 patients, with the usual doses of 16 mg. of morphine sulfate, indicated that the antithrombin test does not become positive after this quantity of opiate has been administered.

In conclusion, I should like to again congratulate Dr. Machella on his excellent and very thorough paper and for the privilege of being permitted to discuss it.

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Medical Management of Pancreatitis

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The therapy of pancreatitis is neither standardized nor specific, and often it is disappointingly ineffective. Certain trends in therapy are, however, noticeable. During the last two decades the treatment of acute pancreatitis has emphasized nonoperative supportive and symptomatic measures in the early phases of the disease. General adoption of this plan has been attended by an appreciable reduction in the fatalities which formerly resulted. Even so, there remains an apparent irreducible mortality, the magnitude of which is in the neighborhood of 10%.*

It appears that not only is improvement in therapy responsible for the greater survival rate but also improvement in diagnostic procedures has led to recognition of many milder, relatively innocuous, instances of the disease which previously would have been undiagnosed. Not only does this mild acute pancreatitis have a low mortality rate, but patients with severer forms of the disease also recover more frequently than formerly.† Kirby and his associates [8] have directed attention to a changing cause of death in acute pancreatitis as a consequence of improved therapy and longer survival. In patients treated before 1946 death resulted early from circulatory collapse, while in those treated after 1946 survival was longer and death resulted most frequently from secondary hemorrhage and sepsis. Considerations of this sort justify speculation as to methods of attack on this residual mortality. Since the high mortality which accompanied early surgical intervention in acute pancreatitis was attained during the period when effective antimicrobal therapy was not available and the nature of the disease less well understood, the suggestion that a more aggressive early surgical approach be carefully reevaluated [5] has appeal.

A further consequence of improved diagnosis and increased recovery from acute pancreatitis is the recognition that chronic recurrent forms of the disease are much commoner than was previously realized. Studies by Comfort and his associates ‡ of recurrent pancreatitis indicate this to be a sequacious event in the total disease, leading in many instances to defunctionalization of the organ's endocrine and exocrine activities. Fortunately, this chronic end-stage of the disease, with its diabetes, steatorrhea, creatorrhea, and malnutrition, is rare, but the chronic relapsing pancreatitis is not an uncommon occurrence.

The problem of pain control in chronic pancreatitis is a serious one, since medical management often is unsatisfactory and many patients seek escape from the realities of the disease in alcoholism or narcotic addiction. Many surgical procedures have been devised and applied to the treatment of chronic pancreatitis for this reason. No one of these procedures has proved universally successful. Appreciation of the fact that recurrences are frequent has led to more careful attention to measures, both medical and surgical,

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* References 1 and 2.

† References 3 and 4.

‡ References 6 and 7.

aimed at recognition and elimination of the causes of these recurrent attacks, with rewarding results.

MEDICAL MANAGEMENT OF ACUTE PANCREATITIS

Although it is generally agreed that acute pancreatitis should be treated conservatively,§ a number of patients still require exploration in order to establish a diagnosis. This is a relatively harmless procedure, provided operative manipulation is held to the minimum. The serious consequences of errors in diagnosis of the morbid states with which acute pancreatitis may be confused justify adoption of this attitude. When the diagnosis of acute pancreatitis can be made with confidence, by whatever means, regardless of the degree of severity of initial manifestations, it is best to apply in full the principles of conservative treatment in every instance, because of the unpredictability of the clinical course of the disease.‖ No distinction is made between the treatment of primary acute pancreatitis and that of recurrent acute attacks of the disease.

Medical management of acute pancreatitis is directed toward (1) relief of pain, (2) treatment of shock and replacement of fluids and electrolytes, (3) temporary suppression of pancreatic secretion, (4) prevention and control of distention, (5) prevention of suppuration, (6) management of disturbances of carbohydrate metabolism, (7) detection and management of surgical complications, and (8) prevention of recurrences.

Relief of Pain

Control of the agonizing, unrelenting pain of acute pancreatitis is of prime consideration, not only because of the great anguish it produces but also because of the vasoconstricting effect of severe pain itself.[12] When important structures are involved, the ischemic phenomena may determine a fatal issue. A variety of pharmacologic and mechanical measures are available to effect control of pain. Their number and diversity should warn against the adoption of too sanguine an attachment to any one of them. Use of a combination of these various measures often is required to effect satisfactory relief.

Analgesic Agents.—Morphine sulfate, 10 to 15 mg.; dihydromorphinone (Dilaudid) hydrochloride, 2 to 4 mg., and meperidine (Demerol) hydrochloride, 100 to 150 mg., have proved useful. These agents relieve pain by their central action. Morphine and its derivative dihydromorphinone possess the more powerful analgesic and sedative actions, but they increase tension in the smooth muscle of the digestive tract and pancreaticobiliary ductal apparatus, facts which have diminished enthusiasm for their usage. Because of their marked capacity to produce addiction, these agents are particularly unsuited for use in repeated and frequent recurrences of pancreatitis.

Nonopiate analgesics, although less addicting and less depressant, are also less effective. Meperidine hydrochloride often is recommended as the analgesic of choice for use in pancreatitis, but it also increases tension in the musculature of the upper gastrointestinal tract and sphincter of Oddi, though to a lower degree and of shorter duration than the opiates. Even so, typical attacks of biliary colic following administration of merperidine hydrochloride have been known to occur in persons with disease of the biliary tract.¶ The spasmolytic effects of this agent are mostly confined to the lower intestinal tract.[13]

Intravenous administration of 0.1% solution of procaine hydrochloride has been used for relief of pain of acute pancreatitis,[10] but the analgesia obtained is highly variable, and unpleasant or dangerous side-effects are not infrequent.#

Agents Acting Directly on Smooth Muscle.—Spasm of the duodenal musculature, the sphincter of Oddi, and the pancreaticobiliary ductal apparatus often is considered as either a primary inciting or a contributing

§ References 1 and 8-11.

‖ References 8 and 9.

¶ References 13 and 14.

References 8 and 14.

factor in the development of episodes of acute pancreatitis.[16] Relief of spasm in the upper digestive tract becomes an important consideration, not only from the standpoint of relieving pain but also as a rational measure designed to influence the course of the disease. Measures to relieve this spastic element may be directed at the muscle itself. Inhalation of amyl nitrite,* sublingual administration of 0.4 to 0.6 mg. of glyceryl trinitrate (nitroglycerin),† or the intravenous administration of 250 to 500 mg. of aminophylline,[21] (theophylline ethylenediamine) all have a very salutary muscle-tension-relaxing effect in the structures involved, even when this tension has been increased by the use of morphine or other analgesics. Unfortunately, duration of the effect of these agents is short and on occasion the presence of hypotension renders their use injudicious. Calcium gluconate administered intravenously in amounts of 10 to 20 cc. of a 10% solution, although primarily directed at correction of deficiency of calcium salts in the blood, also is reported to have a valuable antispasmodic effect.[22] Further attack on the spastic and other phenomena contributing to pain in pancreatitis may be obtained by use of the following group of agents, whose action is at the effector cells of the autonomic nervous system.

Autonomic Blocking Agents.—Two groups of these autonomic nervous system blocking agents have proved useful. The sites of their action are diverse. The first group exerts its principal action at the site of the effector cells supplied by the parasympathetic nerves, namely, at the smooth muscle and the exocrine gland cells. Their action is parasympatholytic. Atropine sulfate, 0.4 to 0.6 mg. parenterally,‡ repeated at three- to four-hour intervals, is a well-known and effective agent of this type.

Methantheline (Banthine) bromide is an effective postganglionic blocking agent, particularly useful in the management of pancreatitis, since its action on the upper gastrointestinal tract is marked.§ Administration of 100 mg. of methantheline bromide intravenously or intramuscularly occasionally may relieve the pain of pancreatitis without use of narcotics. Usually, however, this good fortune is not encountered. It produces a depressant effect on motility and on the tension of ductal and upper intestinal tract musculature as well as secretory depression of the stomach and pancreas. Propantheline (Probanthine) bromide exhibits similar marked upper digestive tract effects. It, also, is an effective adjunct in the management of acute pancreatitis when given parenterally in 15.0 to 30.0 mg. doses. When either methantheline or propantheline is given intravenously it should be administered in the form of a slow intravenous drip. Each of these drugs may be repeated at six-hour intervals. The mechanism by which these agents relieve pain resides in their capacity to suppress gastric and pancreatic secretion and relax ductal and duodenal muscle spasm. These agents also have a ganglionic blocking action, but it is weak and probably not significantly achieved by the usual dosage employed.[26]

Autonomic blocking agents of the second group exert their principal action in the autonomic ganglia, where they effectively interrupt transmission of both sympathetic and parasympathetic impulses. Tetraethylammonium (Etamon) chloride given slowly intravenously in a dosage of 2 to 5 cc. of a 10% solution has been useful in the treatment of acute pancreatitis.‖ Its clinical effectiveness rarely lasts longer than an hour, unfortunately, and while intramuscular administration prolongs effectiveness, this route of administration requires injection of large amounts of fluid and is painful. In general, methonium compounds are more effective blockading agents. Hexamethonium (Bistrium) bromide, 250 mg. every 12 hours, administered by gavage, has been

* References 8, 10, and 16.

† References 18-20.

‡ References 8, 10, 20, 23, and 24.

§ References 8, 10, 20, and 25.

‖ References 8, 10, 20, and 27.

useful in certain instances.[28] Irregular responses to this agent, owing to erratic absorption, seem to interdict this route of administration in acutely ill subjects. Parenteral administration of hexamethonium bromide has a more predictable response. In the acutely ill subject a maximum of 25 to 50 mg. of the salt given in fractional amounts slowly intravenously, while the blood pressure is being measured frequently, has been effective. This dosage may be repeated after four to six hours. The occurrence of hypotensive syncope is not a problem in therapy with hexamethonium compounds in acute pancreatitis, since these patients are maintained in a horizontal or slightly head-down position. Caution against hypotensive episodes should nevertheless be exercised. Even the presence of hypotension does not render unwarranted the use of blockading agents, and measures detailed later for the control of shock are effective after their use.

The exact mechanism by which pain is relieved by these agents is uncertain. Afferent visceral pain impulses probably are inhibited, but the depressant effect on secretory activity of the stomach and pancreas along with the inhibition of ductal and upper intestinal muscle spasm and motility also may be invoked to explain the salutary effect.

Mechanical Measures for Control of Pain.—Paravertebral sympathetic and splanchnic nerve block ¶ often are employed to relieve the pain of pancreatitis. Paravertebral nerve block is accomplished by the injection of 1% solution of procaine hydrochloride bilaterally into the paravertebral area in the interspaces from T_5 through T_{12}. Unilateral and bilateral splanchnic nerve block is advocated by many and is accomplished by the injection of 20 to 30 ml. of 1% procaine hydrochloride solution into the loose areolar tissue anterior to the body of the first lumbar vertebra.

Epidural anesthesia has its advocates # and seems to be a most effective method for the control of pain. This is accomplished by the introduction of a 3½ gauge ureteral catheter into the epidural space at the level between L_1 and L_2 and the subsequent maneuvering the tip of the catheter upward until it lies in the neighborhood of the interspace between T_5 and T_6. Here the catheter is permitted to remain until the need for pain relief has vanished. Anesthetic solutions can be injected through the catheter as required. This method can be especially helpful in frequently recurring attacks of chronic pancreatitis, since its use obviates employment of addicting opiate and nonopiate analgesics during such episodes.

Advocates of these methods of pain relief claim a high degree of success in relief of pain. Presumably pain relief is obtained by interruption of impulses in the visceral afferent nerves which subserve the transmission of pain stimuli. Despite the fact that efficient obtunding of pain is obtained often by use of these methods, it is unlikely that their use influences the course of the disease, since a fatal termination may occur even though pain has been satisfactorily abolished.

Treatment of Shock and Fluid Imbalance

Hypotension, decreased blood volume, and hemoconcentration are common accompaniments of acute pancreatitis.* Overt shock, often associated with severer degrees of pancreatic necrosis, fortunately is much less common.[23] At least a part of these phenomena as well as the attendant depletion of electrolytes results from vomiting, transudation of fluids or hemorrhage into the peritoneal cavity, and effects of extravagated pancreatic enzymes into the abdomen or the peripheral blood stream.

For the treatment of overt shock, transfusions of whole blood, administration of 100 to 200 cc. of 25% normal human serum albumin [11] solution, and dextran solutions, as well as other fluids, may be required. Administration of normal human

¶ References 22, 23, 27, 29, and 30.

References 30-32.

* References 11 and 23.

serum albumin has much to recommend it. Not only does it have a salutary effect on replacement of blood volume [11] but it is thought to have an antitryptic activity also.[33] The vascular collapse induced by hypertrypsemia justifies cautious use of levarterenol (Levophed) bitartrate as a slowly administered dilute solution. Cortisone acetate intramuscularly has been useful in certain instances,† and when the need is urgent hydrocortisone (Cortef), 100 mg. diluted in isotonic saline, may be given intravenously. It has seemed to be lifesaving in two personally observed instances. Measurement of blood pressure and hematocrit value and establishment of a normal urinary output indicate adequate treatment of shock.

Repletion of electrolytes is best accomplished under close laboratory control. However, reduced sodium, potassium, calcium, and chloride concentrations occur with such regularity [36] that their replacement may be undertaken empirically. Lactated Ringer's solution and Darrow's solution, both of which are available commercially, are convenient forms for administration of these electrolytes. Not only the initial losses of fluid and electrolytes must be replaced but also those resulting from continuous nasogastric suction. Renal function is impaired in acute pancreatitis more frequently than is generally realized.‡ When oliguria occurs, caution must be exercised in the amount of fluid given and the administration of solutions containing potassium salts. Losses of calcium are great so that additional supplies of this ion must be furnished in the form of 10 to 20 ml. of a 10% solution of calcium gluconate once or twice daily, as recommended for relief of muscle spasm.

Suppression of Pancreatic Secretion

The temporary suppression of pancreatic function is attained by mechanical and pharmacologic devices designed to eliminate the neural and hormonal stimulants of pancreatic secretion. All food and drink is withheld during the acute period. A soft Levin tube is passed into the stomach, and the tip is accurately located near the pylorus. Continuous gentle suction is applied except for such brief hiatuses as may be required to administer drugs by gavage. This application of constant suction prevents appreciable amounts of acid gastric juice from entering the duodenum and decreases formation in the upper small intestine of the hormonal stimulant to pancreatic secretion. Administration of those parasympatholytic and ganglionic blockading agents recommended for controlling pain also depresses acid secretion in the stomach and further aids in elimination of the acid chyme from the duodenum. These agents also directly suppress the neural stimuli to pancreatic secretion.

The beneficial results reported from x-ray therapy [39] in acute pancreatitis find some support in the experimental demonstration of dimunition of pancreatic secretion in animals by the application of this method.[40] However, the awkwardness of administration of this therapy to severely ill patients, the availability of other effective methods of control, and the unknown late effects of irradiation leave little to recommend this method of therapy.

Control of Distention

Abdominal distention due to the presence of ileus in acute pancreatitis is frequent and may present a serious problem, impelling prompt therapeutic attention. Usually nasogastric suction will eliminate distention; however, it may occasionally be necessary to intubate the small intestine in order to relieve this symptom.

Management of Derangements of Carbohydrate Metabolism

Elevations of blood sugar to diabetic levels are not uncommon with primary attacks of pancreatitis,[41] but they more frequently occur with or following the acute episodes of the chronic relapsing form of the disease.§ Glycosuria is common in pancreatitis, but the need for insulin therapy is shown by the concentration of glucose in the blood, which

† References 34 and 35.

‡ References 37 and 38.

§ References 1 and 7.

is also the best guide to the amount required. The amounts of glucose solution administered in acute pancreatitis should be carefully controlled, and when frank diabetes is present the chary use of insulin will be required. This caution in the use of insulin is necessary because of the well-known parasympathomimetic effect of hypoglycemia and because the rapid disappearance of blood sugar under the influence of insulin may aggravate an existing hypokalemia. Especial caution to avoid insulin reaction is indicated when ganglionic blockading agents are employed, since the sympathetic blood-glucose-mobilizing mechanism is inoperative.

Prevention of Suppuration

Despite the fact that a bacterial or viral agent as a frequent cause of pancreatitis is unlikely, experimental studies indicate that certain micro-organisms contribute to the fatal outcome [42] in acute disease. Furthermore, the late development of suppuration in the pancreas and other sites in the peritoneal cavity from secondary infection of devitalized tissue is well-known. These clinical and experimental studies prompt the early and vigorous administration of antibiotic therapy in every instance of acute pancreatitis. Administration of 600,000 units of penicillin procaine intramuscularly every 12 hours along with oxytetracycline (Terramycin) hydrochloride or chlortetracycline (Aureomycin) intravenously in a dosage of 0.50 gm. repeated at 6-hour intervals usually will adequately suppress the offending organisms. Although experimental evidence indicates oral administration to be more effective, this route often is not feasible because of vomiting, ileus, or the use of constant suction.

Application of these principles of supportive therapy will result in the uninterrupted recovery of many patients with pancreatitis, but should evidence of spreading peritonitis, marked edema and bulging in the flanks, acute cyst formation, or deepening jaundice appear then appropriate surgical intervention is required. Recent evidence [3] that late hemorrhage is a frequent cause of death in acute pancreatitis indicates particularly the necessity of prompt adequate surgical drainage of tender abdominal masses. Definitive surgical procedures are best delayed until the acute attack subsides.

Termination of Treatment

The decision to discontinue therapy must be based on an appreciation of the clinical signs of improvement. Abrupt discontinuation of all therapy should not be undertaken. When pain has subsided and analgesic drugs no longer are required, when the pulse rate and temperature have returned to normal limits, when distention has disappeared and bowel sounds have returned, and when the over-all appearance of the patient warrants, cautious discontinuation of therapeutic measures and oral feedings are begun. With the nasogastric tube in place, suction is discontinued and small feedings of broths, cream soups, skim milk are started. Antiacids between feedings are routine. If pain does not ensue with the first few feedings, the nasogastric tube is removed. Mild sedation in the form of oral administration of phenobarbital, 30 mg. three times daily, is wise, and either methantheline or propantheline bromide is continued by mouth three times daily. As rapidly as is tolerated, the diet is increased to a bland one given in six small feedings a day. The bland six-meal diet, a sedative given three times a day, and the administration of an antispasmodic drug should be continued indefinitely.

Prevention of Recurrences

No program for the management of pancreatitis can be considered as adequate unless ample attention is devoted to the prevention of recurrences. My own experience indicates that recurrences should be expected, as a rule. This concept is supported by the many studies of patients with acute pancreatitis who have been subject to previous acute episodes.‖ And it is these repeated attacks with piecemeal destruction of the pancreas that eventuates into the fibrosis and calci-

‖ References 2, 9, 10, and 23.

nosis of the gland with its associated clinical phenomena of malnutrition, steatorrhea, creatorrhea, and diabetes.

The prevalence of biliary tract disease in association with attacks of acute pancreatitis makes careful investigation of the entire biliary apparatus mandatory. Furthermore, investigation of the upper gastrointestinal tract for lesions, such as diverticula, which might occlude the pancreatic ductal apparatus may occasionally yield fruitful results. Appropriate definitive surgical treatment must be carried out when mechanical factors are demonstrated. Available evidence indicates that this type of therapy is highly effective in the prevention of recurrences.[43]

The frequent association of acute attacks of pancreatitis with the ingestion of large quantities of food or drink, or both, indicates interdiction of alcohol and the prudence of ingesting reasonably sized meals as prophylactic measures. Other gastrointestinal irritants and stimulants should be avoided. A program of mild sedation combined with antispasmodic and alkali therapy and bland small frequent meals has appeared to be helpful in some instances.

MEDICAL MANAGEMENT OF CHRONIC PANCREATITIS

Recurrent attacks of acute pancreatitis are a prominent part of the clinical picture of chronic pancreatic disease. The management of the acute episode in no way differs from that of the primary acute attack. Each acute attack should lead to a consideration of and search for a cause of the recurrence. Medical preventive measures as previously detailed should always be attempted. However, these measures frequently are not adequate, and recurrences occur in spite of efforts to prevent them.

The meager success of medical therapy in controlling recurrent attacks of pancreatitis has led to the development of many surgical procedures for the treatment of chronic pancreatic disease.¶ These procedures range in their scope from those designed to control pain only to complete extirpation of the pancreas. It is not within the scope of this paper to discuss these procedures, but it appears that those measures designed to prevent pain alone are the least satisfactory and those which involve internal drainage procedures are somewhat better.[5] Operations for the relief of pain alone afford only temporary relief, and within a period of months pain not infrequently recurs, but with diminished intensity.

During the progress of chronic relapsing pancreatitis the development of frank diabetes mellitus should always be suspected. Glucose-tolerance curves should be accomplished periodically during pain-free intervals in order that diabetes may be detected early. When diabetes occurs it is usually mild, and its treatment in no way differs from the management of diabetes unassociated with pancreatitis, unless pancreatic insufficiency also is present. Care should be taken to avoid insulin reactions. Diabetes becomes more of a problem when pancreatic achylia exists simultaneously, when the problem of maintenance of nutrition is an additional serious problem.

Maintenance of nutrition in chronic pancreatitis is difficult to accomplish. The diet should provide about 30 to 40 Cal. per kilogram for the normal expected weight based on age, height, and bone structure. At least 75% of the calories should be furnished in the form of carbohydrate and protein. Protein should be allowed in the amount of about 100 to 150 gm. per day. Meals should be divided into six feedings. Often it is advantageous to furnish a part of the daily protein requirement as a partial hydrolysate. Supplemental vitamin therapy, particularly the fat-soluble vitamins, should be provided in ample quantity.

Administration of pancreatin in the form of enteric-coated tablets in the amount of 5 to 10 gm. three times a day is occasionally helpful. Likewise, administration of purified preparations of bile salts in amounts of 0.3 gm. three times in a day and sorethytan (20) monooleate (Sorlate), 1.5 gm. three times a

¶ References 5, 30, and 44.

day, may help promote fat absorption. Choline, methionine, or other lipotropic substances may be recommended empirically in an attempt to prevent development of fatty liver.

SUMMARY

A conservative comprehensive program for the supportive, symptomatic, and antibiotic therapy of acute pancreatitis is outlined. Measures aimed at the prevention of recurrences are stressed. Management of chronic pancreatitis emphasizes control of painful attacks and surgical measures to interrupt progress of the affection. In the later stages of chronic pancreatitis maintenance of nutrition and the control of metabolic disturbances are the chief features of medical management.

ABSTRACT OF DISCUSSION

DR. J. EDWARD BERK, Detroit: Dr. Jones, in a fashion typical of him, has presented a comprehensive and thorough review of the principles underlying the present-day medical treatment of acute and chronic pancreatitis. I can add nothing. The over-all management of pancreatitis, however, transcends medical treatment alone. Moreover, it is associated with many problems, most of which are still unsettled. While these problems are not properly within the scope of Dr. Jones' presentation, they seem pertinent to the topic and are in keeping with the tenor of today's considerations. I should like your permission, therefore, to devote the time allotted to me to a consideration of some of these problems.

Patients are met in whom a precise diagnosis of acute pancreatitis cannot be established despite the use of all diagnostic procedures. One is perforce required to subject such patients to exploratory laparotomy. In such circumstances, my colleagues and I have developed the practice of employing epidural block as the anesthetic for the operative procedure. In the event that acute pancreatitis is found, the indwelling catheter in the epidural space is permitted to remain and fractional instillations of an anesthetic agent are then introduced as often as may be necessary to control pain.

From time to time one sees a patient who presents clinical and laboratory features not only of acute pancreatitis but also of acute cholecystitis. At times the acuity of the cholecystitic process demands emergency operation. Our general attitude in such cases, however, has been ultraconservative. It has been our impression that these patients do better if operation can be postponed at least until the acute pancreatitis has subsided somewhat.

The patient with chronic pancreatitis who has continuing pain and the patient with frequently recurring episodes of acute pancreatitis present particularly perplexing problems. It is easy to decide in such instances that medical management alone is ineffective and that some more radical approach is necessary. The problem arises, however, in selecting the approach, for one is faced here with what is veritably a therapeutic nightmare. The very fact that so many different surgical procedures are available for use in the treatment of chronic pancreatitis is eloquent testimony in itself that no single procedure is effective in all instances. The operative procedure currently in vogue seems to be sphincterotomy. While recent-day experience with this operation has not extended over a long period of time, sufficient evidence has already accumulated to indicate that it, too, is not a panacea. A very serious question exists, in my mind at least, whether sphincterotomy should be employed uncritically or whether it should be reserved for use only in patients demonstrating evidence of obstruction at the papilla or reflux into the pancreatic duct or both. I concur in Dr. Bockus's viewpoint that little or nothing would appear to be gained by doing sphincterotomy routinely in addition to cholecystectomy in patients with chronic relapsing pancreatitis who also have cholelithiasis. It has been my experience, as it has been his, that many of these patients do quite well after cholecystectomy alone. Indeed, there is some evidence in the literature to indicate that some patients with frequently recurring acute pancreatitis may do well after cholecystectomy even if their gall bladders are free of stones and apparently normal.

These, then, are but some of the problems that beset us. Their solution will require reliable data upon which sound judgment may be based and a more intelligent therapeutic approach formulated.

DR. SOLOMON G. MEYERS, Detroit: I enjoyed Dr. Jones' paper. There is a discrepancy between the mortality rate in acute pancreatitis quoted by Dr. Jones and that presented by Dr. Bockus. According to the former, 10% of the patients receiving medical management died, while the latter has cited a figure of 1.6% mortality.

In a series of 127 patients with acute pancreatitis studied at the Detroit Receiving Hospital by Drs. Brown, Boone, Henderson, and myself, the mortality with medical treatment was 16%. The medical mortality was found to be directly related to the severity of the pancreatitis. With a preponderance of patients with necrotic and hemorrhagic types of pancreatitis the mortality was higher. Many of these cases in our series came to autopsy.

When the patient was not very ill and recovered, it was presumed that acute edematous pancreatitis was present.

In an acute abdominal catastrophe, one must be quite certain of the diagnosis of pancreatitis if one is to limit the treatment to medical measures. Otherwise, major surgical conditions in the abdomen would not receive the proper treatment. The history and physical findings in acute pancreatitis are very similar to those in major surgical catastrophes. The laboratory procedures, as mentioned by Dr. Machella, can be misleading. The x-ray findings of sentinel ileus and basilar atelectasis so beautifully demonstrated by Dr. Bockus this afternoon are not specific for pancreatitis. Moreover, the mortality from operating on these patients when exploration was the only procedure done was 17% in our hands, which was comparable to the medical mortality. Therefore, if there is any doubt about the presence of an abdominal catastrophe which would be benefited surgically, there should be no hesitation in operating on such a patient.

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SYMPOSIUM ON RESPIRATORY DISEASES

Current Concept of the Finer Structure of the Lung

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A prodigious amount of research has clarified many of the problems of lung structure at both gross and microscopic levels. The structural components of the larger elements of the respiratory tree are adequately described in current textbooks of histology; there is little disagreement concerning them. However, as the respiratory areas of the lung are approached, structures become increasingly delicate and their delineation becomes correspondingly more difficult. The point of greatest contention and the one most difficult to settle has been the question of whether or not the pulmonary alveolus is lined by a continuous epithelium. During the past century, hundreds of authors have applied a multitude of technical procedures in attempts to solve this problem and have arrived at conflicting conclusions as to the nature of the alveolar surface.

Since an understanding of normal and abnormal pulmonary physiology and a rational approach to the treatment of lung diseases must have as their basis a thorough knowledge of the minute structure of the lung, this question is of more than academic interest.

The trachea and primary bronchi and the generations of branches to which they give rise, including the bronchioles, serve primarily for the passage of air to and from the respiratory areas of the bronchial tree. Admittedly, these can be sites of serious disease; yet the majority of clinical entities which profoundly affect normal pulmonary physiology, such as bronchiectasis, pulmonary emphysema, pulmonary edema, asthma, hyaline membrane disease, et cetera, involve more peripheral portions of the bronchial tree. In view of their importance and of new information which is available concerning them, the present considerations are limited to the terminal airways of the lung.

Because limitations of space preclude an historical review or even a fair coverage of the literature, a few recent special works on the lung are cited below, in which the extensive bibliographies will serve as an introduction to the literature.* This, then, is not presented as a review article in the usual sense but is rather an attempt to give a concise account of the structures comprising the true respiratory areas of the lung. Special emphasis will be placed upon the structure of the pulmonary alveolus considered in the light of some recent work on the much-debated question of its lining. The definition of a few terms will be helpful in the development of the following account. For discussions of the terminology of indi-

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vidual parts and concepts of their arrangement in groups the reader should consult the works of Miller [1] and of von Hayek.[3]

THE UNIT OF CONSTRUCTION OF THE LUNG

The Acinus.—An old concept of the acinus (Rindfleisch) as the final division of the bronchial tree has been shown to be incorrect and is falling into disuse. It is mentioned here simply because it may be encountered occasionally in the literature. The acinus as originally described consisted of from three to five alveolar ducts representing aborizations of very short terminal bronchioles. Anywhere from 2 to 30 such acini could constitute a lobule (secondary lobule, as defined below).

The Secondary Lobule.—This is sometimes referred to simply as a pulmonary lobule, although the complete term should be used to distinguish this unit from the smaller primary lobule, a designation which is widely used. Both are useful terms and will be defined here.

Repeated bronchial branching results in progressively smaller airways, and those which have a diameter of less than 1 mm. are arbitrarily called bronchioles. These bronchioles enter at the apices of roughly pyramidal secondary lobules, in which they continue to branch and give origin to elements described in the paragraph about the primary lobule. The pyramids vary greatly in height and diameter of base. Since bronchioles may take many directions, it follows that their pyramids are variously oriented. Those whose bases face the pleura trace polygonal outlines upon it and contribute to the mottled appearance characteristic of the lung surface. The secondary lobules in some species (pig, ox, man) are bounded by connective tissue septa which extend from the pleural connective tissue at their bases to the dense sheath of the bronchioles at their apices. In animals such as the rat, cat, rabbit, and dog, which have a very thin pleura, no septal prolongations of the subserous connective tissue layer are produced and so the secondary lobules are not separated from each other. Such septa, when present, serve to delimit lobular disease and to restrict the extension of subpleural blebs.

Primary Lobules.—The bronchiole upon entering a secondary lobule produces additional generations of branches within it leading to terminal bronchioles. The branches of the latter differ from ordinary bronchioles by the presence of small outpocketings, or alveoli, on their walls. Accordingly, these are termed alveolar or respiratory bronchioles (Fig. 1). There may be one or several orders of respiratory bronchioles, the last of which branches into long hallways, or alveolar ducts, bearing many alveoli. The next order of branches, described by Miller [1] in the cat, dog, and man, arises from the distal end of the alveolar duct in the form of one to six approximately spherical enclosures called atria. These, however, are not described by all workers. Atria give rise to a variable number of projections,

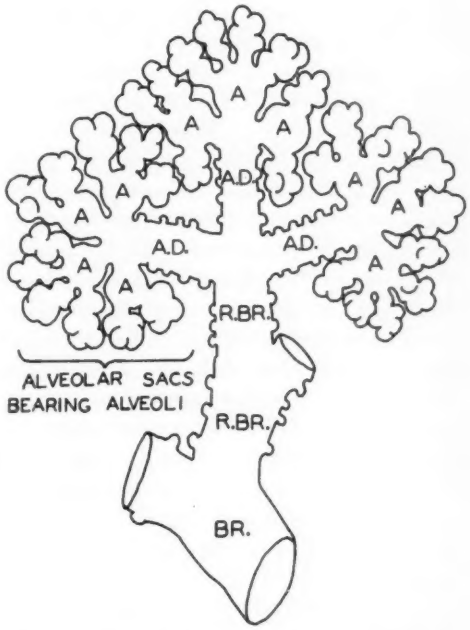

Fig. 1.—Schema showing the formation and relationships of the last orders of branches of the bronchial tree. (Based on a diagram by W. S. Miller, "The Lung," Charles C Thomas, Publisher.[1]) *A*, atria; *A.D.*, alveolar ducts; *Br.*, bronchiole; *R. Br.* respiratory bronchiole.

the alveolar sacs, which bear the terminal alveoli. The unit of structure shown in Figure 1, consisting of an alveolar duct, atria, alveolar sacs, and alveoli, plus their accompanying nerves, blood, and lymph vessels, is the primary lobule of the lung.

STRUCTURAL ELEMENTS OF PULMONARY LOBULES

Bronchioles.—Although bronchial branches of less than 1 mm. are considered bronchioles, a criterion other than size would be desirable. The diameter as measured in a section is certain to be different than that in the living lung. There is an initial collapse of the lung when it is removed, involving primarily the smaller airways, followed by shrinkage produced by the action of fixing agents. The degree of shrinkage will depend in some measure upon the fixative used and the method by which it is applied (immersion; intrabronchial instillation, with or without pressure).

The walls of bronchioles are characterized by a high proportion of muscle, but they are devoid of cartilage. Bronchioles and their branches enter the substance of the respiratory tissue, and so they are attached all about to the elastic spongework of the lung. Thus, upon inspiration, they are subjected to a circumferential pull, obviating the need for cartilaginous rings to maintain an open bronchiolar lumen. At the same time, the absence of cartilaginous supports permits an occlusion of the lumen by the contraction of the bronchiolar smooth musculature.

Passing peripherally, we find that the epithelial cells of the lining are reduced in height. Glands, fortunately, are scarce or lacking here, for an accumulation of secretion in such small tubes might cause a serious blockage. The membrane lies upon an elastic lamina propria with elastic fibers running parallel to the long axis of the tube. External to this is the muscular layer, supported by connective tissue.

Respiratory Bronchioles.—Terminal bronchioles produce the next order of branches, the respiratory bronchioles, so called because of the presence of alveolar respiratory elements upon their walls. At the transition from bronchiole to respiratory bronchiole the cells of the epithelial lining decrease in height from columnar to cuboidal. In sections, however, the epithelium is seen only along stretches of the bronchiolar wall which lie between adjacent alveolar entrances. At the termination of the last in a short series of respiratory bronchioles the cuboidal epithelium suddenly attenuates and seems to disappear so that the airways distal to this point appear to have little or no epithelial lining.

Alveolar Ducts.—The next order of branches arises from a respiratory bronchiole as two or three and sometimes more elongated passages named alveolar ducts. They have extremely delicate linings, and the walls are deeply indented by the bands of smooth muscle that surround them. Alveolar ducts are the most peripheral airways to possess muscular components. The elastic fibers, however, continue peripherally to the terminals of the bronchial tree.

Like doors entering upon long corridors, except that here they are present also in floor and ceiling, are the openings of numerous alveoli which beset the walls of alveolar ducts. The alveolar ducts terminate in rotunda-like spaces, the alveolar sacs. Some workers, notably Miller,[1] would interpose a stage, the atrium, between these two (Fig. 1). Miller has described atria in the cat, dog, and man, but authors of current textbooks of histology and monographs on the lung either neglect to mention them or else allude to them as "minutiae." Further study seems warranted to clarify the status of the atria.

Alveolar Sacs.—A variable number of more or less spherical spaces surmount the tips of alveolar ducts, and these are the alveolar sacs (Figs. 1 and 2). Their walls are thin, consisting primarily of a rich capillary net lined by an extremely thin epithelium, supported by elastic fibers, reticulum, and a few collagenous fibers, but they are devoid of smooth muscle.

Fig. 2.—An alveolar sac, cut at its opening into an atrium. Elastic fibers encircle the junctional area and form a network about the sac. Semidiagrammatic. (From W. S. Miller, "The Lung," Charles C Thomas, Publisher.[1])

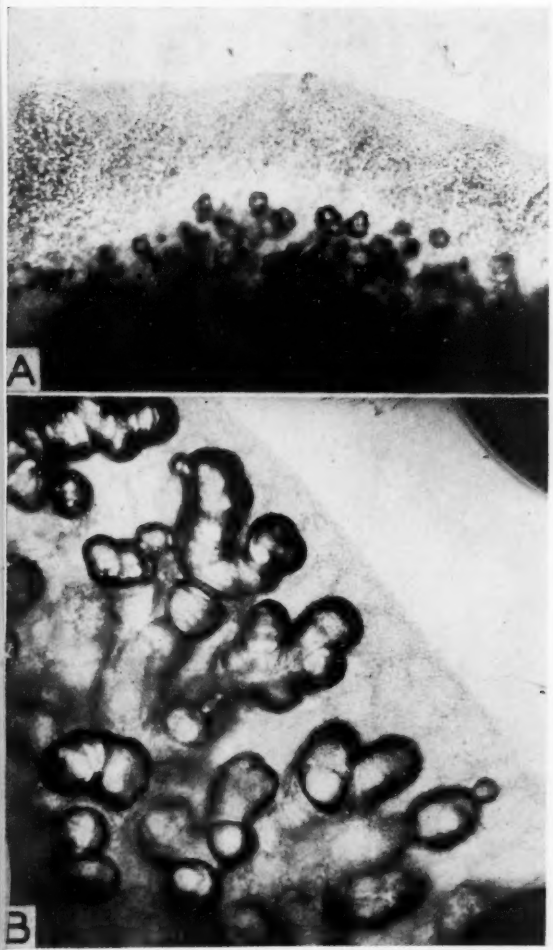

Fig. 3.—*A*, peripheral area of fresh lung of newborn mouse prior to inflation in transparent lung chamber. Partially collapsed airways extend into peripheral zone of primary atelectasis. *B*, comparable area of a lung of similar age after redistention of collapsed airways and inflation of more distal, previously atelectatic branches of respiratory tree. Note plump, rounded normal contours and size of the airways. Both *A* and *B* were photographed at the same magnification; × 75.

In the more proximal divisions of the bronchial tree elastic fibers run mainly parallel to the long axis of the airway and thus are put on the stretch longitudinally, but those fibers which extend out into the walls of alveolar sacs and alveoli form complex networks which both prevent overdistention in the absence of smooth muscle and preserve the shapes of these structures (Fig. 2).

Alveoli.—The terminals of the bronchial tree, borne by the alveolar sacs, are the alveoli (Fig. 2). Usually three or four alveoli are found on each sac. One does not gain a true impression of the shape of the alveolus or, for that matter, of any of the finer airways from plastic reconstructions of fixed sections. The walls of the sac seem folded and collapsed, as indeed they must be, and the alveoli appear as irregular bulges between the folds. To see the normal contours of the respiratory bronchioles and the branches distal to them it is necessary to examine fresh lungs that have been redistended to their normal size. This has been done by placing the lungs of young mice in a sealed transparent chamber in which they are gradually reexpanded under negative pressure and observed microscopically.† Such a lung is shown in the collapsed and partially inflated conditions in Figure 3.

In the lung of a newborn mouse, only the central portions are inflated at first. Peripheral areas remain atelectatic for a week or more, and the distal generations of branches already formed in them are gradually entered and expanded by air. This process can be accelerated in the lung chamber, and the inflation of each new order of branches can be followed and photographed, as in Figure

† References 5-11.

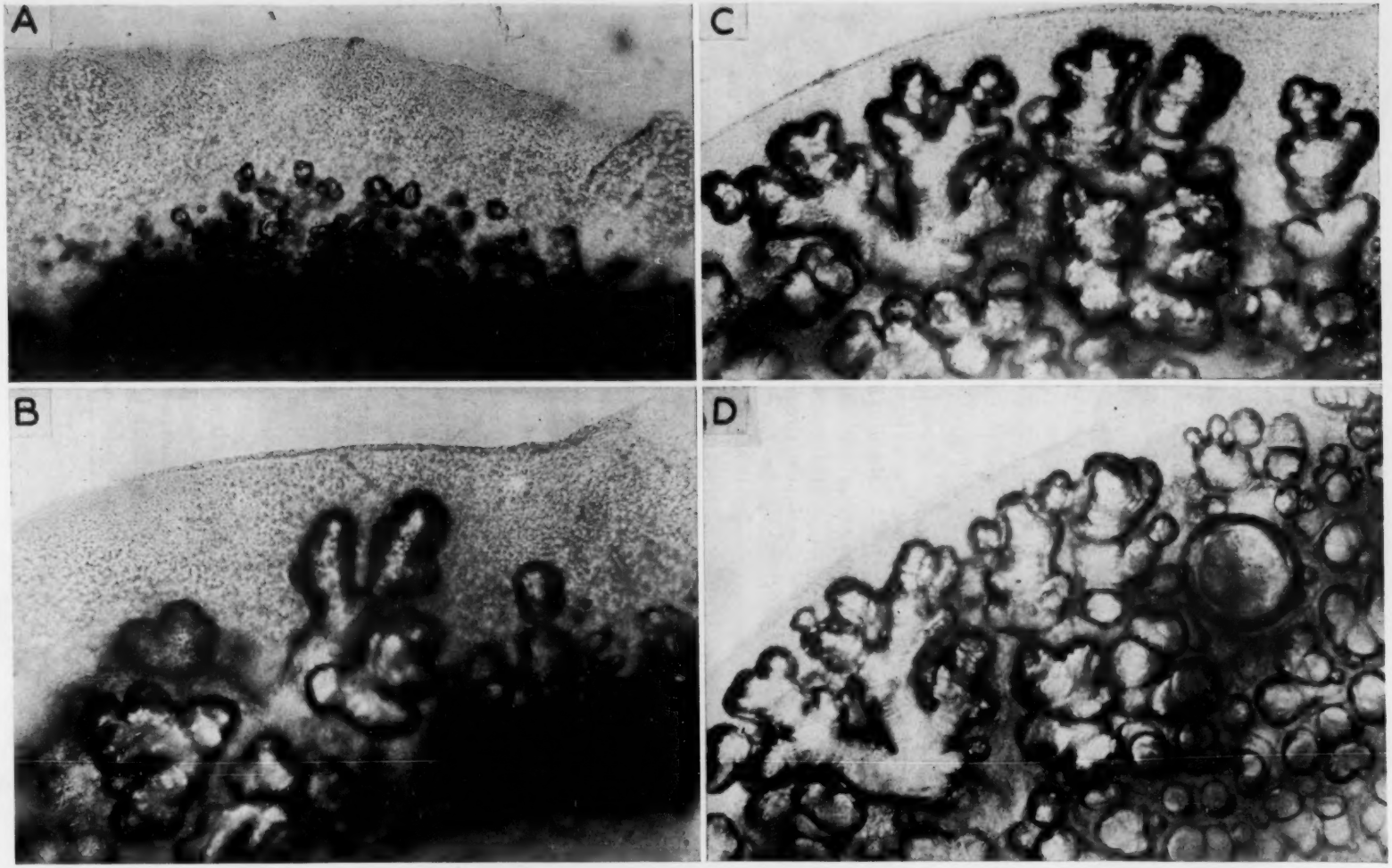

Fig. 4.—Peripheral area of newborn mouse lung in transparent chamber. The marginal zone is completely atelectatic. *A* to *D* show progressive stages in the inflation of terminal airways as lung is subjected to negative pressure. *A*, prior to inflation. Spaces previously expanded in normal respiration are collapsed, but retain some air. *B*, previously expanded airways are redistended, and air enters distal branches to expand them. *C*, additional generations of alveolar ducts are expanded. *D*, expansion is nearly complete. On left are alveolar ducts, alveolar sacs and alveoli; lower right shows alveoli just beneath cover slip. Large sphere at upper right is a bubble between lung and cover slip; × 80.

4, or recorded in motion pictures.[7] It permits studies on the mode of branching, number of branches, and their mutual relationships and sizes without resorting to the tedious technique of plastic reconstructions. Moreover, the terminals are displayed in their normal, plump rounded contours and not as irregular collapsed spaces.

When they are examined at higher magnification the relationship of alveolus to alveolar sac may be seen. The terminal alveoli are shaped like shallow bowls, that is, they open widely into the cavity of the sac (Fig. 5). This arrangement favors the aeration of alveoli, since air moves at its slowest rate in terminal passages and it can eddy in and out of a wide alveolar mouth more readily than it might through a constricted orifice.

Fig. 5.—An alveolar sac near the ventral margin of the lung, bearing subpleural alveoli. Note wide alveolar openings into sac. Drawn from a projected frame of a motion picture taken of a freshly removed mouse lung during expansion with air in the lung chamber.

Alveoli are similar in construction wherever they are found (on respiratory bronchioles, alveolar ducts, or alveolar sacs). The walls, like those of alveolar sacs, consist primarily of a rich capillary network which is, in the last analysis, the true lung. All other structures in the lung are there merely to serve the pulmonary capillaries, as conduits for air, for support, and to maintain a clean respiratory surface. The alveolar epithelium (about which more will be said later) rests upon a network of reticulum which is interwoven about the capillaries. There is also a network of elastic fibers mentioned previously and a few collagenous fibers, but the chief framework of alveolar walls is the network of surface and internal reticulin membranes.[12] Smooth muscle is absent, since muscle bands are found

peripherally only as far as the ends of alveolar ducts. The alveoli borne by alveolar ducts and respiratory bronchioles do not derive muscular elements from them. The openings of such alveoli, however, are encircled by smooth muscle bands, and to this extent they differ from terminal alveoli. Postmortem changes and fixation shrinkage may account for the somewhat constricted entrances seen in alveoli which open into air tubes. For a discussion of the physiologic role of these muscular entrance rings, see von Hayek.[3]

LUNG DEVELOPMENT AND THE NATURE OF THE ALVEOLAR LINING

Concerning the controversy over whether or not the alveolus has a continuous epithelial lining, new evidence is rapidly accumulating which should soon settle this century-old debate. The pertinent literature is too voluminous to be adequately covered here, but the few articles cited below will serve as an introduction to it.

The investigators whose work has led them to conflicting conclusions may be divided into two principal groups. The one believes that the postnatal alveolar walls have no continuous epithelium and that the capillaries are indeed as naked as they seem upon microscopic examination. The second group, while differing as to the special features of the cells involved, feels that there is a continuous epithelial alveolar lining, but one which, by reason of its extreme thinness, is extremely difficult to demonstrate.

One's concept of the adult alveolar surface is determined in large measure by his views on lung development. Here again, there have been differences of opinion. In its early development the lung consists of a system of branching epithelial tubes of endodermal origin that form the linings of the future branches of the bronchial tree. Mesenchymal condensations around the tubes furnish the connective tissue elements of the walls. Around the fifth month of development structures corresponding to alveolar ducts and alveoli appear at the tips of branches. At this stage the lung is compact, not spongy, and, microscopically, it closely resembles a tubuloalveolar glandular structure. The epithelial cells vary from columnar to cuboidal and form a continuous layer throughout the tubes.

What happens during the last one-third of gestation has been argued extensively. Many workers, among them Flint,[13] Bender,[14] Bensley and Groff,[15] and Cooper[16] have held that the glandular nature of the lung is retained until about the time of birth. Then the bronchial tree is greatly expanded by the influx of air, with the result that the lining cells of the terminal branches are stretched out from a cuboidal to an extremely thin squamous type. According to this view, then, the squamous cells would still form a continuous lining for alveolar ducts, sacs, and alveoli in the postnatal lung. Opposed to this view are Stewart,[17] Palmer,[18] Barnard and Day,[19] Clements,[20] and Ham and Baldwin,[21] who report that in the later stages of gestation the epithelial lining of the terminals becomes discontinuous, permitting naked capillaries to rise to the surface between the separated cells. This would mean that after birth the structures of mesenchymal origin in alveolar walls would come in direct contact with the inhaled air. In other words, a condition of normal or physiologic interstitial emphysema would exist in the lung tissues. The implications carried by this second view are discussed by Ham in his textbook.[22]

It occurred to me that the fate of the continuous prenatal epithelium might be learned by observing the alveolar lining while the alveolus underwent its initial expansion. The mouse lung was selected because of its small size and translucence. It was then discovered that while the proximal airways were well-opened prior to birth the peripheral ones remained atelectatic for a time postnatally. When the fresh lungs of newborn mice were examined during expansion with Ringer-Locke solution, the cuboidal epithelial cells of the atelectatic alveoli were seen to stretch, flatten; then suddenly (more rapidly than the eye could follow) the mem-

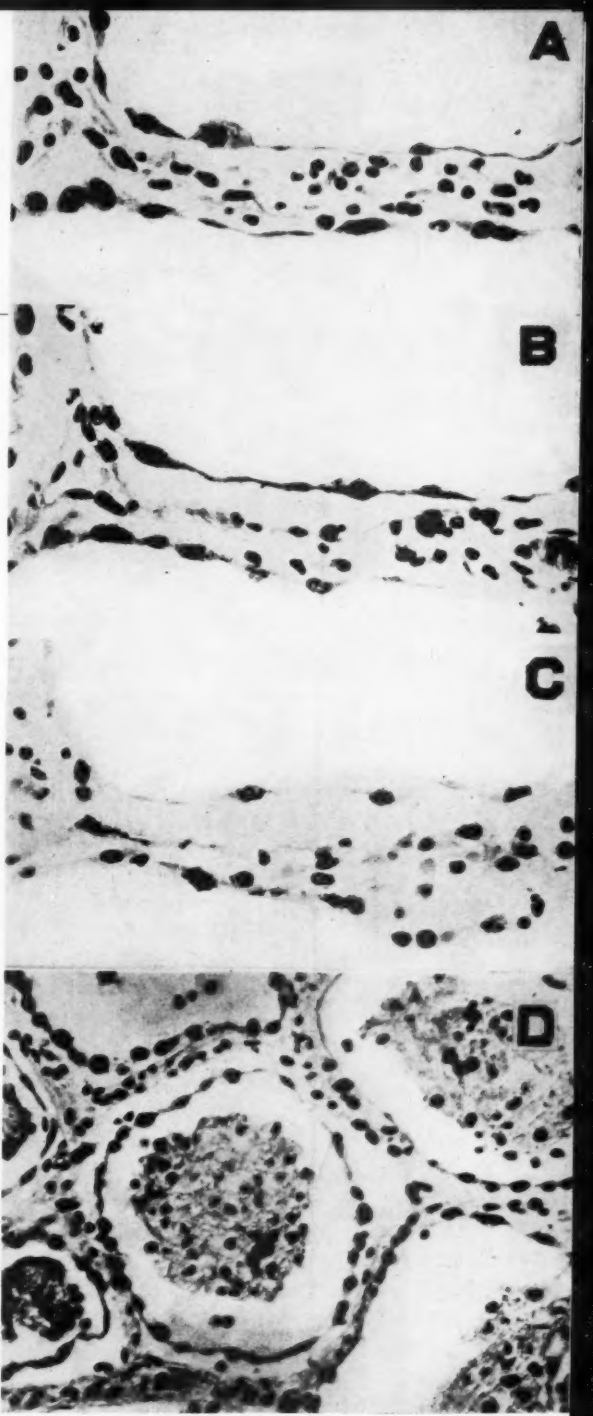

Fig. 6.—Examples of the epithelial lining of alveolar walls, pushed off as a continuous sheet by serous exudate in cases of pneumonia and mitral stenosis (*A*, *B*, and *C*, × 440; *D*, × 250). (From W. S. Miller, "The Lung," Charles C Thomas, Publisher.[1])

brane appeared to lose its identity as a continuous layer of cells, leaving only what seemed to be isolated cells spaced along the walls. These were recognized as the well-known septal cells, or epicytes. In the intervals between them lay apparently naked capillaries.

It is difficult indeed to believe blindly in the existence of an invisible structure, and many have simply concluded that the alveolar surfaces of pulmonary capillaries are naked. Others, through various lines of reasoning, special staining, tissue culture, reference to pathologic material, and by experiments have attempted to prove otherwise. Miller,[1] for example, has found thin epithelial membranes apparently raised off the alveolar walls by an accumulation of serous exudate in cases of pneumonia and mitral heart disease (Fig. 6) as well as alveoli lined by cuboidal epithelium in cases of bronchopneumonia, interstitial pneumonia, and in Hodgkin's disease. Cowdry [23] shows photomicrographs of the lungs of sheep afflicted with a tumor-like disease in which there is a hyperplastic alveolar epithelium. While such evidence suggests that these membranes represent displaced and swollen, or hyperplastic, epithelium which is normally much thinner, it loses some force by reason of the pathologic nature of the material. Attempts to raise the alveolar epithelium in mammalian lungs by producing pulmonary edema through the introduction of agents such as alpha-naphthyl thiourea (ANTU) have not been successful.[24]

However, examples of detached alveolar epithelium in normal mammalian lungs are not wanting. Bensley and Groff,[15] for instance, in a paper reporting the persistence until term of cuboidal alveolar epithelium in rat fetuses, found that successive inspirations just before and after birth stretched the epithelium into a thin membrane. Under certain conditions, such as moderate distention of the lung, delayed or differential fixation, or by moderate maceration and some good luck these authors could display the epithelial membrane lifted off the capillaries of the alveolar wall. Miller,[1] too, found evidence of a continuous alveolar epithelium in im-

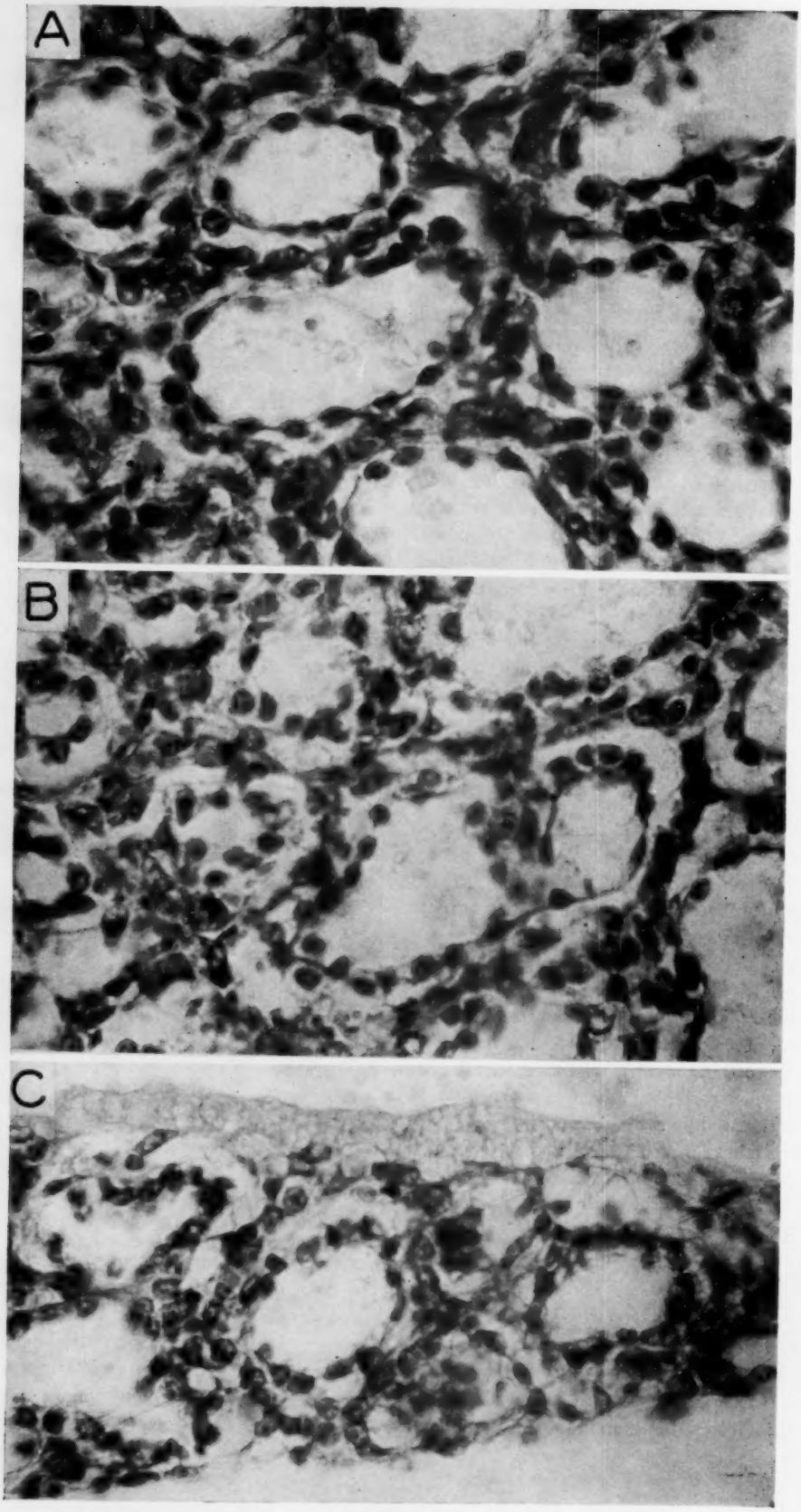

Figure 7

(See legends on opposite page)

perfect sections. He shows a torn section of a normal partly collapsed lung with the alveolar epithelium pulled off as a continuous sheet. My findings in late fetal and newborn mice [25] closely parallel those of Bensley and Groff [15] in the rat. As mentioned above, the newborn mouse lung has peripheral areas of primary atelectasis in which the alveoli are lined by continuous cuboidal epithelium, persisting for some days following birth. As the expansion of the terminal airways proceeds gradually from central to peripheral, the atelectatic zone is progressively reduced and finally disappears in about a week. It was expected that during this period there should exist areas of transition from the seemingly unlined air spaces to those retaining their cuboidal epithelial linings, and such areas were sought. In the preparation of some late fetal and neonatal lungs for sectioning there evidently occurred some deviations from our usual technical procedure. The result was a series of badly shrunken and distorted lungs which, by ordinary standards, were poor indeed. Yet the violent shrinkage of the epithelium which occurred proved most interesting and instructive.

Figure 7 illustrates the lungs of fetuses one day prior to birth and of animals which had breathed for one day. These lungs show cellular alveolar linings in various degrees of attenuation. They are graded in thickness from cuboidal cells, through stages wherein they are more flattened, down to the merest films of cytoplasm, and sometimes the entire transition can be made out in a single alveolus. That the epithelium is a continuous one is easily seen because the entire layer of cells, regardless of thickness, has been shrunken away from the capillaries and other contents of the alveolar walls. It is likely that the extreme attentuations seen in some areas, if closely applied to a capillary wall, would appear to be capillary endothelium alone when viewed with the conventional microscope. Undoubtedly, additional examples of such raised epithelium could be supplied by others who have had similar experiences. Such findings support Miller's belief that the raised epithelial membranes found in cases of pulmonary edema represent the original alveolar linings pushed off the walls and swollen by the serous exudate beneath.

The concept of naked pulmonary capillaries has been struck a telling blow by the beautiful electron photomicrographs of alveolar walls published by Low.‡ These pictures (Fig. 8) show that the alveolar epithelial cells, or epicytes, which are distributed over the alveolar walls actually send out long fine cytoplasmic extensions which cover the alveolar surfaces of the capillaries. These attentuated portions of the cells vary in thickness, but they measure on the average 0.2μ and sometimes only 0.02μ. Thus, there is an epithelial alveolar lining, as many have suspected, but since its attentuated portions are at or beyond the practical limits of resolution of the light microscope, it is only rarely that the epithelial continuity can be appreciated with this instrument.

Epicytes, Septal Cells, and Alveolar Epithelial Cells.—The terms epicyte and septal cell are often used interchangeably to denote the apparently isolated cells, easily seen with an ordinary microscope, which are scattered about the walls of pulmonary alveoli. The cells may rest on the alveolar surface and bulge slightly into the alveolar lumen or

‡ References 26 and 27.

EXPLANATION OF FIGURE 7

Fig. 7.—Photomicrographs of mouse lungs in which the shrinkage caused by reagents has separated the alveolar epithelial lining from the alveolar walls. *A* and *B* show deeply placed alveoli; *C* is a section through a thin marginal portion of the lung showing subpleural alveoli. *A*, fetus, 20th day. Note continuous alveolar epithelium. *B*, an adjacent section of the same lung, showing a wide range in the degree of attenuation of the epithelial cells. *C*, newborn, one day old. Alveoli in peripheral areas retain a cuboidal epithelium for about a week following birth. The epithelium here shows less cytoplasmic attenuation than in *A* and *B*. Formalin 10%, hematoxylin and eosin; × 900.

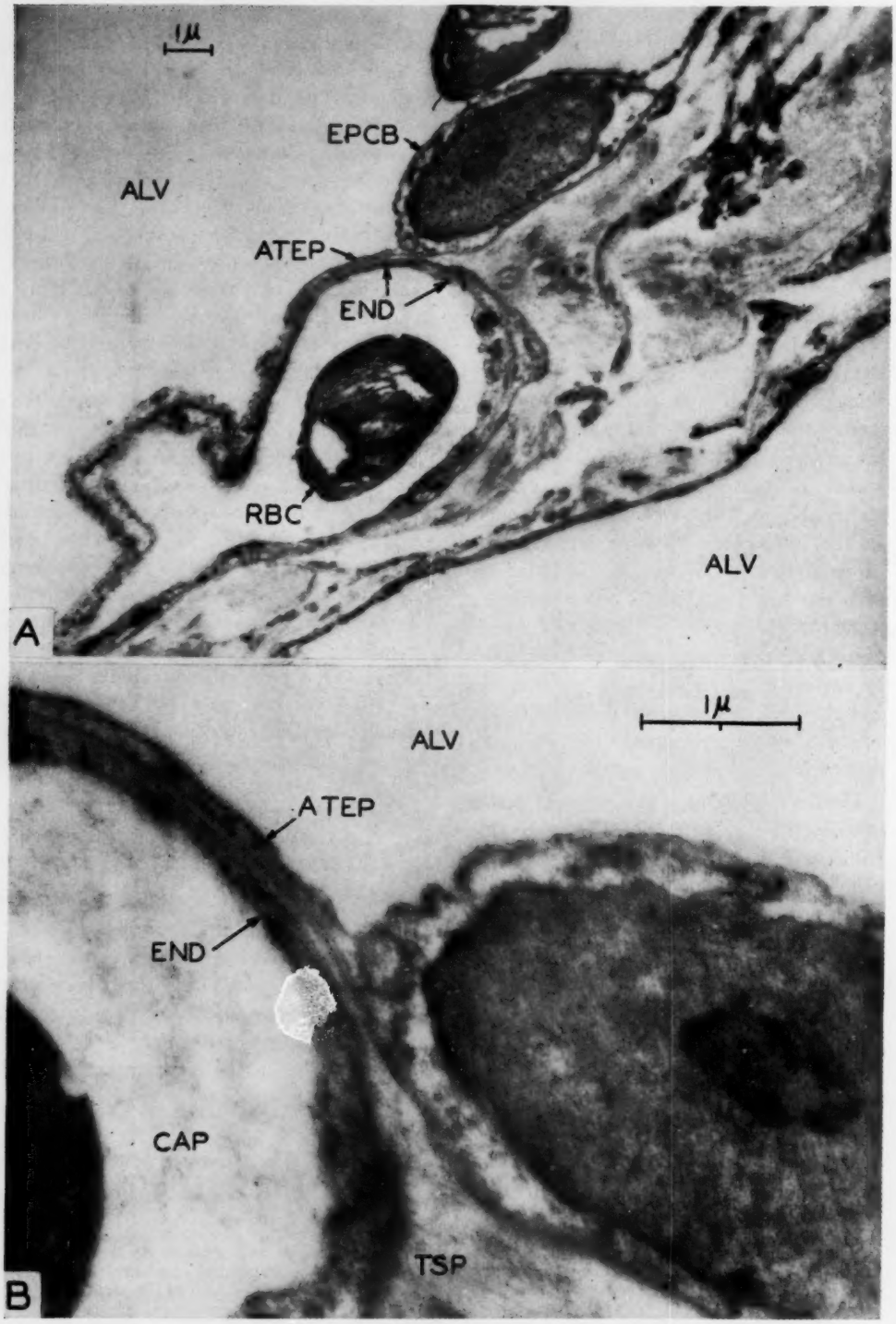

Figure 8

(See legends on opposite page)

else be embedded or countersunk into the alveolar wall. Their cytoplasm has a rather granular appearance owing to the presence in it of numerous clear "vacuoloids." The term septal cell is not an apt one, since the cells in question occur not only upon the interalveolar partitions or septa but upon the marginal bases of subpleural alveoli. Both terms have been used extensively, in particular by those who view them as isolated cells, separated by distances occupied by naked capillaries. Consequently they have come to connote individual cells and not components of a continuous sheet of tissue. In the face of actual electron photographs of the nucleated epithelium which lines pulmonary alveoli of various mammals, including man,§ even the most ardent adherents of alternate views of alveolar structure must at last admit its presence. These pictures together with various pieces of direct and indirect evidence, forceful arguments presented by Miller,[1] Cowdry,[23] and others, plus some personal observations [25] have convinced me of the reality of the alveolar epithelium. The so-called epicytes, then, are not remnants of a once continuous membrane, or "residual" epithelial cells, but are the thicker parts of cells which form a continuous alveolar lining. Only the portion of the epicyte containing the nucleus and perinuclear cytoplasm is ordinarily visible, since, as mentioned above, the cytoplasmic attenuations lie at or below the practical limits of resolution of the light microscope. If the term epicyte is understood to mean a cell taking part in the formation of the pulmonary alveolar epithelium, there should be no objection to its use. However, for complete clarity it would seem best to simply call the cells in question pulmonary alveolar epithelial cells, for this is what they are.

Alveolar epithelial cells are extremely plastic and adaptable. They appear to have a number of roles, the chief of which may be to serve as the first line of defense of the respiratory surfaces under adverse conditions. Their efficiency in absorbing liquids and gases is well known, and there is some evidence that they may also have a secretory function. That epicytes may enlarge and proliferate to form visible membranes has been reported by a number of workers. Macklin,[2] among others, has considered them to be capable of remarkable metamorphosis into larger cells which may rest on the alveolar walls or be set free in the alveolar space. Some of these have been termed alveolar "foam cells" because of the appearance of the cytoplasm, rich in vacuoloids. Some foam cells are usually found in normal lung sections if carefully sought, and many others are probably lost from alveolar lumens in carrying out the histologic techniques. I have seen numerous cells having the cytoplasmic attributes of foam cells in alveoli of fresh intact lungs. Their production is apparently stimulated by infective agents, for they are abundant in certain diseased lungs. They may be real or potential phagocytes. Macklin [2] has found them in intermediate stages which link them with the well-known "dust cells" of the lung, which are undoubtedly phagocytic. Being free, dust cells laden with ingested particles may move along the nonciliated passageways until picked up and propelled upward and outward by the mucus stream present in the more proximal branches of the bronchial tree.

§ References 26 and 27.

EXPLANATION OF FIGURE 8

Fig. 8.—Electron micrographs of alveolar wall, human lung. *A*, epithelial cell body (EPCB) on upper surface of alveolar wall attenuates abruptly into a cytoplasmic prolongation (ATEP) which covers the underlying capillary; × 7200. *B*, the epithelial cell and capillary of *A* at higher magnification to show greater detail at the point of attenuation. The distinction between attenuated epithelium (ATEP) and capillary endothelium (END) is best seen near the epithelial cell body where the tissue space (TSP) just beneath it is prolonged for some distance between the epithelium and the capillary wall; × 25,000. (From Low, F. N.: *Anat. Rec.* **117**:241-263 [Oct.] 1953.[27] Courtesy of Dr. Frank N. Low, Louisiana State University School of Medicine, and Dr. Edmond J. Farris, Executive Director of the Wistar Institute of Anatomy and Biology, Philadelphia.)

In freshly removed lungs of newborn mice, expanded with Ringer-Locke solution and observed for an hour or more, I have seen alveolar epithelial cells round up, become more prominent, release themselves from the wall, and drift about in the fluid-filled lumen. Numerous large free cells are a regular finding in the peripheral alveoli of mouse lungs at birth, and they increase in number from 1 or 2 to as high as 10 per alveolus during the first week of life. They are usually found embedded in or resting upon masses of tiny globules which are always present at this time,|| as if in the act of devouring them. The source and significance of these globule masses require further investigation. Also deserving of further study is the question of whether all alveolar phagocytes are of endodermal epithelial origin or whether some may be ordinary macrophages and thus belong to the reticuloendothelial system. Their relative quantities in healthy and diseased lungs and possible differences in their behavior are subjects of interest.

SUMMARY AND CONCLUSIONS

The lung is an organ which serves primarily to bring air quickly into intimate relationship with a large quantity of blood, permitting a rapid transfer of respiratory gases from one to the other. The rich pulmonic capillary networks, therefore, are the important structures in the lung, and all of its other components are there merely to serve them as supporting mechanisms, as conduits for the gases, to keep the respiratory surfaces clean and in good repair, and to serve as defense mechanisms.

Prior to birth the epithelial linings in many of the finer airways begin to stretch and thin out in preparation for postnatal respiration. The more peripheral areas of the lung are the last to become prepared in this way, and their epithelial attenuation may not be achieved until some days after birth. Postnatally, the respiratory areas of the lung are lined by a layer of epithelium which, although extremely fine, is continuous with that lining the more proximal portions of the bronchial tree. The cuboidal epithelium of respiratory bronchioles attenuates abruptly at the mouths of alveoli borne by them and at the points of branching of respiratory bronchioles into alveolar ducts. A great portion of the lining membrane is too thin (0.2μ and even less) to be distinguished with the conventional microscope. Only the thicker portions of the epithelial cells, containing the nucleus and perinuclear cytoplasm, are usually visible. These visible portions, considered by some as entire cells, have been called septal cells or epicytes. Being modified elements of the original epithelial lining of the bronchial tree, the alveolar epithelial cells are endodermal in origin.

The cells which line the alveoli are very adaptable and versatile; they can adjust to varying degrees of alveolar expansion and proliferate and enlarge in disease and in response to various noxious agents. Individual cells of the alveolar epithelium can undergo metamorphosis and be transformed into larger free cells when the need arises and exhibit phagocytic properties. Such modified cells are sometimes found occupying openings in interalveolar septa (alveolar pores). Dust cells often contain numerous inclusions of foreign particles and undoubtedly represent an important means of removing particulate matter from airways distal to those furnished with other methods of eliminating fine debris (cilia, mucus). Some of the phagocytes which appear in the air spaces may not be of endodermal origin, as are those just mentioned, but may be ordinary macrophages and thus belong to the reticuloendothelial system.

Since the terminal air spaces of the lung are lined by epithelium, they should not be considered to be sites of a normal interstitial emphysema. Those who hold the view that alveoli are spaces within connective tissue explain the production of new generations of terminal branches of the respiratory tree as

|| References 6, 8, and 11.

an infiltration of air into this tissue, resulting in the opening up of new spaces. But, with the demonstration of a cellular alveolar lining, a more reasonable explanation of the postnatal growth of new airways would be a proliferation of the lining cells and an outgrowth of new alveoli from the existing spaces.

The knowledge that there is a continuous cellular alveolar lining will aid in explaining the rapid production of epithelial membranes in a number of pulmonary diseases. It should also influence the thinking of those concerned with the administration of medication through the inhalation of mists and of those interested in the irritating and possible carcinogenic influences of smokes and other inhaled particles upon the pulmonic membranes.

The present understanding of pulmonary anatomy and physiology is far from complete, and the unanswered questions concerning lung growth, phagocytosis, pulmonary circulation, and the effects of ageing on pulmonary structure and function, to mention just a few fertile areas for study, require attention. With fine instrumentation, histochemical techniques, electron microscopy, and other research implements already at our disposal and others sure to follow, the lung offers some challenging and attractive opportunities for further investigation.

ABSTRACT OF DISCUSSION

DR. JULIUS LANE WILSON, Philadelphia: Dr. Krahl's new technique and the resulting observations have furnished new information about the lung which may prove to be of clinical importance. This advance added to the demonstration with the electron microscope by Low proves that a true alveolar epithelium does exist, although it is so thin as to be invisible to the ordinary microscope. The opinion of William Snow Miller, that such an epithelium must exist, has been verified. We must henceforth think of the functions and disease states of a peculiar type of body cell, the alveolar epithelial cell.

This cell, with its extremely attenuated cytoplasm, stands guard between the intercellular spaces of the body and the hostile outside world as it extends into the alveolus of the lung. Air freely admitted into the tissue spaces might cause perpetual interstitial emphysema. Moreover, the naked capillaries require protection from the endless bombardment of molecules of the gases which fill the alveoli as well as from the particle of dust, the spore, the bacterium, or the virus occasionally penetrating to the alveolus. The police action of the phagocytes, whether they originate from the epithelial cells themselves or from the blood, must be called into play, if possible, before invasion of the tissues rather than after.

It is now easier to understand the absorption of soluble medications administered by aerosol. The fine droplets, reaching the alveolus and wetting the surface of the alveolar epithelial cells in a monomolecular layer, are readily transferred across that ultrathin membrane to the capillaries. At the same time, the capillary wall and the intercellular spaces are protected against particles and colloids or oils.

The alveolar epithelial cell is the obvious source of alveolar-cell carcinomas. Although relatively rare, this type of malignant growth is of particular interest, because its further study may throw some light upon the etiology of new growths. Sometimes called adenomatosis of the lung, this tumor is distinguished by its apparent multicentric origin in the lungs in some instances. Since the alveolar portion of the lung has no lymphatics, the spread of such a new growth must be either direct or via the bronchi. Morphologically, alveolar-cell carcinoma is very similar to the communicable disease of sheep called *jaagziekte*. Is this a possible link between virus-caused diseases and malignant tumors?

No benign tumor due to the proliferation of alveolar epithelial cells has as yet been described, as far as I know, but it is a safe predication that pathologists will find such a tumor as they become more familiar with this previously unrecognized cell.

In the pulmonary changes due to beryllium poisoning we have a beautiful example of the selective action of a noxious agent on one cell—in this case the alveolar epithelial cell. The alveolar epithelium becomes thickened. There results a progressive loss of ability to perfuse O_2 and CO_2 across the membrane, as shown by pulmonary physiologic studies. There is no corresponding decrease in the ventilatory function of the lung, the reverse of the physiologic changes in cases of pure interstitial fibrosis. The patient dies of beryllium poisoning when the barrier of thickened epithelium seals his pulmonary circulation away from the life-giving atmosphere. Possibly other industrial agents, as yet unsynthesized or still on the chemist's shelf, will also affect the alveolar membrane. Certainly other clinical applications of the new fundamental knowledge contributed by such workers as Dr. Krahl will be forthcoming.

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Some Fundamentals of Respiratory Physiology

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There are many distinct, separate, and interrelated parts to the broncho-pulmonary-circulatory system that make up the complex organs of respiration. We can delineate the function of each portion and determine how these are related to each other. By this means is created a composite picture of respiratory function.

If, however, we wish to view respiratory physiology from the standpoint of what is essential to normal, healthy living; what causes impaired function and the symptoms of such pathology, and how to treat these pathological conditions, then we must consider the entire respiratory unit as an adaptive and compensatory mechanism. This, as we shall see, is true in all of the major divisions of respiratory function: ventilation through tracheobronchial channels, gas interchange through the alveolar capillary membrane, circulation of blood through the pulmonary capillary bed from the right heart to the left auricle, and the systemic circulation with gas exchange in the body tissues.

It is well known, for instance, that a sudden collapse of one lung may produce severe dyspnea, cyanosis, and cardiac embarrassment, although the unaffected lung is more than adequate to take care of the burden of respiration. A gradual collapse of the lung, which allows the unaffected side to compensate for the loss of functioning lung, may produce no symptoms at all.

Other, less obvious, compensations occur. If the lung is poorly ventilated because of the inelasticity of emphysema, we may find a quick inspiration and a long-drawn-out expiration, with pursed lips placing the yet retained air under positive pressure. This results in oxygen reaching the alveoli by diffusion during expiration, since the rate of diffusion is much more rapid than the slow velocity of the expiratory current. Or, when the blood contains an insufficient amount of oxygen because of an inefficient alveolar capillary membrane, or for any other reason, the cardiac output may be increased and a larger volume circulated per minute. In the normal person, an output of 4 liters of blood per minute containing 20 vol. % of oxygen carries a total of 800 cc. per minute and delivers about 160 cc. of oxygen to the body tissues. When, under pathological circumstances with 75% saturation of the arterial blood, 16 vol. % oxygen is carried, a compensatory increased cardiac output may result in a circulation of 5 instead of 4 liters per minute. The total amount of oxygen will again be 800 cc. per minute, and, while the body cells may withdraw less oxygen from each cubic centimeter of blood, there is an additional 1000 cc. available and the volume of oxygen delivered may again be 160 cc.

Consequently, within rather wide limits of customary activity, a patient with one or more serious pathological conditions may have no symptoms severe enough to make him aware of his trouble. He has a disease, if you wish, but he is neither sick nor incapacitated as long as the compensatory mechanisms operate and are sufficient. It is when compensation breaks down that symptoms occur, progress, and lead to relative or complete disability. This is the explanation of the comparatively

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short history reported by patients who have emphysema, silicosis, or other slowly developing or long-standing chest diseases. The symptoms are only for that period which follows the loss of compensatory mechanisms.

This understanding of compensation as the prime factor of respiratory physiology is a necessity in therapy. Dyspnea, for example, is a distressing symptom, and its relief might be one aim of successful treatment. But many patients with long-standing emphysema or pulmonary fibrosis have carbon dioxide levels far above normal. Since expiration is the method of eliminating most carbon dioxide and since the kidneys are unable to reduce the acid excess of the acid-base balance, a rapid but inefficient respiration just maintains this carbon dioxide level without being able to lower it. If, in the attempt to relieve dyspnea by oxygen or narcotics, the respiratory rate is slowed too much or too fast, up goes the carbon dioxide to toxic levels, and the patient, relieved of his dyspnea, may relax into coma and death. If the mechanism is understood and the compensatory nature of rapid respiration recognized, therapy will be designed to relieve the distress but maintain the rate of respiration or, by the use of positive-pressure apparatuses, overventilate the lung and eliminate even more carbon dioxide during slow respiration than was eliminated by the fast but inefficient breathing.

This complex of compensations and balances and the equally complex picture of breakdown of compensatory factors explains two common puzzling experiences. The first is that the pathology and the clinical picture frequently bear little relationship to each other. The second is that a regimen which was successful in treating one patient may be of little value for another patient whose disease is apparently similar.

It then becomes necessary to have some definite knowledge of these changes and interferences with function to interpret symptoms and to determine courses of treatment. Sometimes signs and symptoms will point to the source of the trouble. This is true in generalized bronchial infection when bronchospasm and obstruction exist. But when a similar lesion is present only in the small bronchi or bronchioli it is more difficult. For there is no cough reflex this far away from the major bronchi, and, because of the small volumes of air passing through these tiny channels, there may be neither rales nor wheezes. The only symptom will be dyspnea which occurs with mild or continued exertion. But it is also the only symptom of pathology causing inefficient functioning of the alveolar capillary membrane and the only symptom of many pathological changes in the pulmonary circulation.

In the case of the bronchiolar pathology, dyspnea may be relieved by elimination of infection, dilatation of the bronchi, and removal of the retained secretion. But, in alveolar capillary membrane pathology, thickening, which may be temporary, caused by edema or exudation, or permanent, on the basis of fibrosis, has slowed the passage of oxygen through the membrane until the blood barely receives an adequate supply during rest. With any exertion, the oxygen demand is greater and, because of the lung pathology, the rate of flow around the alveolus becomes faster. At the same time, respiration increases in rate but generally becomes more shallow, decreasing the actual percentage of oxygen in the alveoli. Since the passage of gas through a membrane is related to its pressure and the pressure gradient, its solubility, and the thickness of the membrane, we have simultaneous factors for increased and decreased gas exchange. The end-result, however, is decreased exchange, and the arterial oxygen saturation may fall to alarmingly low levels. The dyspnea which develops can be relieved only by a higher concentration of alveolar oxygen.

On the other hand, changes in the pulmonary circulation produce a dyspnea similar to that of heart failure. Normally, exercise causes increased lung ventilation and an increase in pulmonary capillary channels, and, while the cardiac output increases, the pulmonary artery pressure remains the same or even lower than at rest. But in these pathological cases the increased demand for oxygen and blood does not increase the capillary bed sufficiently and additional sclerotic changes

may be present in the arterioles. The pressure then rises to two or three or four times the resting level, which is obviously more than a chronically strained right ventricle can stand. A relative degree of heart failure occurs, with a typical stagnant hypoxia and dyspnea. This will not improve with oxygen alone—it is necessary to do something to lighten the burden on the right heart.

In many cases, all three situations occur at once and each adds interference to the others. If any one is corrected, improvement is noted but lasting progress has not been made. It is for this reason that studies of the right heart and pulmonary circulation must accompany those made of pulmonary function.

When treatment is begun, the first response is generally in the bronchi. The patient feels better, breathes more easily, and will show higher performance in tests measuring pulmonary ventilation. Real improvement comes slowly with long-continued treatment using mechanical as well as pharmacologic aids to respiration. It is necessary to bring inactive lung areas back into function and, with them, alveolar capillaries. This increases the vascular bed, lowers pulmonary artery pressure, and introduces a possible respiratory reserve. This is the goal and rationale for therapy which must be continued for months after symptoms have been relieved.

An understanding of this fundamental adaptive characteristic of the respiratory system brings logic and sense into an apparently confusing picture. Pulmonary pathology may exist and may progress without interfering with the patient or producing any conscious symptoms so long as compensatory mechanisms function. So physicians must learn to recognize these conditions before symptoms occur. Treatment restores compensation early, but it may not affect the underlying pathology for a long time after all symptoms disappear. Therefore treatment must be continued for months or years, regardless of symptoms, in all chronic pulmonary conditions. And in reestablishment of compensatory mechanisms lies the reason for improvement in apparently permanent and irreversible damage to the lungs.

ABSTRACT OF DISCUSSION

Dr. Burgess L. Gordon, Philadelphia: Dr. Levine has mentioned the interrelated units and mechanisms of the respiratory system that participate in pulmonary function, notably, ventilation, gas exchange, and blood flow through the capillary bed.

He disclosed an interesting phenomenon—a sort of compensatory function that takes over the burden of respiration with remarkable effectiveness—as, for example, in slowly progressive atelectasis, when the opposite, or normal, lung meets the challenge to provide adequate ventilation or oxygenation; so effective is this compensatory function that only minimal symptoms, if any, are encountered.

Contrasted are the acute infections or disturbances superimposed in diffuse bilateral disease, such as bronchiolitis and bronchospasm in pulmonary fibrosis. In such instances the symptoms are often out of proportion to the extent of disease and may persist for months if not relieved at the onset.

Dr. Levine has emphasized the very important point that compensation breakdown may occur in chronic pulmonary disease with minimal manifestations. With a failure to eliminate the superimposed condition extreme disability may result. This potential danger calls for function testing and the timely control of the mildest disturbances.

Current Concepts in the Diagnosis and Treatment of Pulmonary Emphysema

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Since Laennec [1] described the clinical and pathological features of pulmonary emphysema, more than a century ago, much has been learned about its pathologic physiology and its progressive clinical course, with cardiac and metabolic complications. However, the initial inciting factors and early pathogenesis still are poorly understood. Because of this hiatus in knowledge, the clinical recognition of emphysema in its early stages is frequently difficult and the results of treatment, once the diagnosis is made, often are disappointing.

DEFINITION

Numerous types of emphysema have been described, as have many concepts concerning their relative clinical importance. Thus, an attempt at definition appears advisable before the clinically diagnostic criteria are considered. Pulmonary emphysema is characterized pathologically by large alveolar spaces with attenuated septa, many of which are fragmented; as a result, larger air spaces (blebs or bullae) are formed, thus altering the mechanical (viscoelastic) properties and ventilation of the lungs, as well as decreasing the reserve capacity of the pulmonary circulatory system. Physiologic studies show expiratory slowing, an absolute increase in the residual volume, and an increased proportion of underventilated alveoli, as well as other less specific changes. The physical diagnostic counterparts of these functional alterations for the most part are demonstrable in the examining room. Dyspnea is the common symptomatic denominator.

Pulmonary emphysema is considered a disease entity, and yet it is frequently seen in association with or following other bronchopulmonary conditions, such as chronic bronchitis, long-standing intractable bronchial asthma, pulmonary tuberculosis, pneumoconioses (such as silicosis), bronchiectasis, and cystic disease involving multiple organs. However, progressive exertional dyspnea without orthopnea often may be associated with no anatomic or physiologic changes other than those of emphysema. Thus, emphysema might be considered the end-stage of the wear-and-tear process on the lung by varied specific diseases or by the mere process of living with environmental factors affecting the person and his variable tissue susceptibility.

The definition just given applies to the so-called diffuse obstructive or "hypertrophic" variety originally described by Laennec. The term "emphysema" has been applied to other pulmonary conditions, which should be mentioned only as a matter of clarification of definition. Localized obstructive emphysema associated with a ball-valve lesion, usually of developmental origin, in infants may be associated with the pathologic changes

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described in diffuse obstructive emphysema in adults, but the changes are usually localized to a single segment, lobe, or lung. Treatment usually consists of excision of the involved tissue, if warranted by the clinical course. "Senile emphysema," or "postural emphysema," is a somewhat nebulous condition in elderly, and sometimes younger, patients who have varying degrees of kyphosis and shortness of breath. An increase in residual volume has been described in some of these patients. Monroe,[2] on the basis of clinicopathologic correlation, has postulated that the thoracic condition is incidental and that dyspnea is usually related to changes in the cardiovascular system, the central nervous system, and the general condition of the body so frequently seen in elderly persons. It is generally accepted, however, that diffuse obstructive emphysema may occur in patients of any age. The term "compensatory emphysema" secondary to collapse or excision of pulmonary tissue would more appropriately be termed "compensatory overexpansion." Simple overexpansion usually is not associated with significantly impaired function. Diffuse obstructive emphysema occasionally may develop in overexpanded pulmonary tissue, but in these cases it is likely that etiologic factors other than simple overexpansion also are present.

DIAGNOSIS

Exertional dyspnea is the most constant clinical feature of pulmonary emphysema. A diagnosis of diffuse obstructive emphysema made in a patient without exertional dyspnea is on tenuous grounds. The onset of dyspnea is usually so insidious and the progress so gradual that several years may elapse before the patient consults a physician. Some patients, however, can relate a rather abrupt onset of dyspnea to a bout of pneumonia or other respiratory infection or to a period of unusual exertion during a hunting trip or an episode of car trouble; in some, it may follow an operation, when an extra load is placed on the reduced pulmonary reserve. Orthopnea and nocturnal dyspnea are conspicuously absent unless concomitant bronchial asthma is associated with attacks of wheezing. In more advanced disease, dyspnea appears to be especially severe when the patient arises in the morning, and the process of shaving and having breakfast is often laborious.

Cough and the production of sputum are not found constantly in so-called pure emphysema, but they usually are present when the emphysema is associated, as it frequently is, with chronic bronchitis, asthma, fibrosis, and bronchiectasis. Christie[3] has stressed the importance of cough in the pathogenesis of emphysema. Wheezing with exertion is frequently noted, even though frank asthma is absent; this type of expiratory obstruction is a well-known characteristic that is associated with an increase in the work of breathing, thus leading to dyspnea. The evidence for this has been reviewed recently by Fry and associates.[4]

As emphysema progresses, patients frequently complain of loss of weight, poor appetite, easy filling at mealtime, bloating, and increased dyspnea after large meals. Patients who have severe emphysema may lose as much as 25 lb. in a six-month period or as much as 50 lb. over many years without any demonstrable intrinsic gastrointestinal disease. The mechanisms of these nutritional symptoms are not well understood.

Results of physical examination with the patient at rest may be entirely normal. The contour of the thorax and measured thoracic expansion frequently are entirely normal even in moderately severe emphysema (Figs. 1 and 2). The classic "barrel chest," or an increase in the anteroposterior measurement of the thorax, described in many textbooks, is a misleading sign. Although frequently present in patients who have significant emphysema, it may be absent. The barrel chest frequently is associated with the kyphosis of increasing age or vertebral changes in the absence of significant pulmonary emphysema or respiratory disability. The measured thoracic expansion is also misleading, since it contributes to only a part of the pulmonary ventilation. Expansion of the thorax may be fairly normal in emphysema, whereas it may

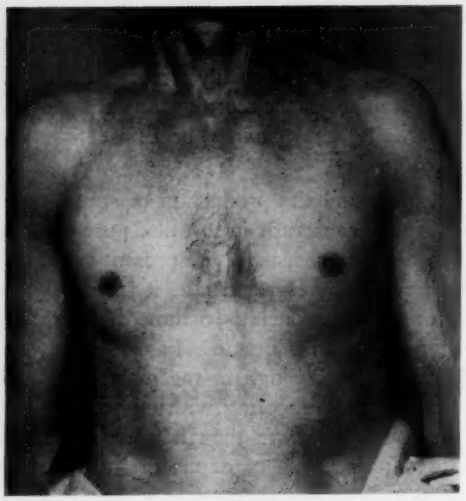


Fig. 1.—Thorax of patient with moderately advanced emphysema. The contour of the rib cage is normal. Thoracic expansion was within normal limits.

be limited in the absence of emphysema, as in rheumatoid spondylitis and neuromuscular disorders.

Demonstration of limited excursion of the depressed diaphragm by thoracic percussion or fluoroscopy probably is a more constant sign of ventilatory disturbance. Auscultation of the thorax with the patient resting may reveal nothing abnormal. In some cases of relatively mild disease, expiratory prolongation or even an expiratory wheeze may be elicited only while the patient hyperventilates or performs a "fast vital capacity" effort. Failure of the breath sounds to increase in amplitude with hyperventilation probably is related to the increased amount of poorly ventilated pulmonary tissue. Exercise tests involving steps can be performed conveniently in the examining room; the patients usually become dyspneic rather suddenly as the ventilation increases. Auscultation over the thorax at this time may reveal the same findings noted during voluntary hyperventilation.

Since the lungs are in a rather constant state of hyperinflation and the diaphragm is depressed, the heart assumes a more vertical and relatively posterior position. Cardiac

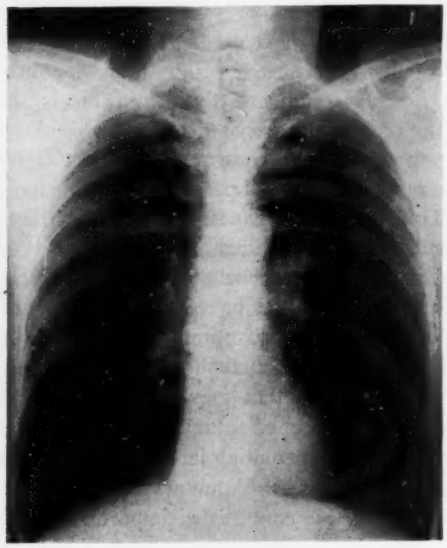
Fig. 2.—Oblique and lateral views of patient pictured in Figure 1.

sounds usually are extremely faint over the precordium, frequently being more distinct and intense over the epigastrium just below the xiphoid process. An accentuated second pulmonic sound may not be easily demonstrated even in the presence of pulmonary arterial hypertension.

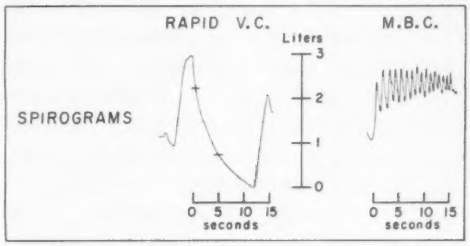
Pronounced cyanosis is a rare finding in uncomplicated pulmonary emphysema. Its presence should alert the examiner to look for complicating pneumonitis, diffuse fibrosis, cor pulmonale with congestive cardiac failure, or a cardiovascular defect shunting blood past the lungs.

Laboratory Tests.—Routine roentgenograms of the thorax taken at full inspiration may show no abnormalities unless the pulmonary parenchyma has been sufficiently altered by the formation of gross air cysts to show variations in radiolucency (Fig. 3). Comparison of roentgenograms taken at inspiration and at expiration or fluoroscopy showing limitation or slowing of diaphragmatic motion gives positive findings at an earlier stage of the disease than do routine roentgenograms.

Fig. 3.—Roentgenogram of the thorax of patient pictured in Figure 1. Although some increased radiolucency is noted in the lower lung fields, there is no widening of the intercostal spaces frequently described as a classic roentgenologic sign of emphysema.



PULMONARY FUNCTION TESTS IN PULMONARY EMPHYSEMA



TEST	NORMAL	———
Vital Capacity (L.)	4.0	3.0
Max. Breathing Capacity (L./minute)	90	42
Max. Midexpiratory Flow (L./second)	> 2.0	0.4
Residual Volume / Total Capacity (%)	< 40	55
7 minute N_2 Index (%)	< 2.5	7.7

Fig. 4.—Results of ventilatory studies on patient pictured in Figure 1. There is pronounced slowing of expiration on the "rapid vital capacity." The reduction of the maximal breathing capacity is greater than the reduction of the "rapid vital capacity."

Secondary polycythemia of a significant degree is an unusual finding in "pure" emphysema, and, like cyanosis, its presence should suggest some complicating lesion. Even in advanced emphysema, the arterial oxygen saturation usually does not decrease to less than 85% and then only with exercise.

The blood carbon dioxide or "alkaline reserve" may be increased only in extremely advanced stages of emphysema, when respiratory acidosis due to retention of carbon dioxide has developed.

Clinical Studies of Pulmonary Function.—The procedures described to measure various aspects of pulmonary function * are too numerous to describe in detail, and many are beyond the scope of this paper. The simple measurement of vital capacity has been shown to be an inaccurate and insensitive indication of impaired pulmonary function in emphysema. A "fast vital capacity" or "timed vital capacity," however, demonstrates the patient's inability to move air rapidly

* Comroe,[5] Vol. 2, pp. 76-244.

out of the lungs. The maximal breathing capacity (amount of air that can be moved in and out of the lungs with maximal voluntary hyperventilation, as measured in liters per minute) may demonstrate this same expiratory slowing (Fig. 4). These measurements can be made directly on a Benedict-Roth apparatus similar to that used to ascertain the basal metabolic rate. The determination of an absolute increase in the residual volume found in patients with emphysema requires the use of complex methods † and is not essential in clinically characteristic cases. Other measurements, such as that of the alveolar concentration of nitrogen after the patient breathes oxygen for seven minutes, likewise are unnecessary in the more clear-cut cases.

Initial Response to Bronchodilator Aiding in Differential Diagnosis of Asthmatic Bronchitis and Emphysema

Test	Predicted Normal Volumes	1/15/55 Before Treatment	1/15/55 After 1 Treatment	1/19/55 After 4 Days of Treatment
Vital capacity, liters	5.0	2.5	3.8	5.1
Maximal breathing capacity, liters per minute	130	34.0	47.0	135.0

Measurement of the "fast vital capacity" and the maximal breathing capacity both before and after administration of an aerosolized bronchodilator may give more detailed information as to the mechanism of ventilatory impairment. The changes in the results of tests after use of a bronchodilator vary considerably among patients who have emphysema and may not correlate quantitatively with the symptomatic response. In general, if the measurements return to within normal range after administration of the aerosol it is likely that the patient has either asthmatic bronchitis or frank bronchial asthma, depending on the clinical features (see Table). If significant improvement in the measurements takes place after the aerosol is used but impairment is still present, a diagnosis of diffuse obstructive emphysema is more likely. However, occasionally intensive treatment with aerosolized bronchodilators is necessary to rule out the reversible element of the patient's disability.

† Comroe,[5] Vol. 2, pp. 188-197.

TREATMENT

Preventive measures probably play as important a role in pulmonary emphysema as they do in other diseases. Early and adequate treatment of those pulmonary conditions complicated by emphysema obviously is of importance. Until the pathogenesis of the "pure" form of emphysema is more adequately understood, prevention is not possible. Once clear-cut signs of emphysema are evident, the process usually progresses to some degree despite concerted medical treatment. However, if treated systematically, some patients may live out the remainder of their normal span of life, finally succumbing to some other disease.

The multiplicity of types of therapy that have been advocated for pulmonary emphysema suggests that no one method is strikingly successful in all cases. Bronchitis, asthma, pulmonary tuberculosis, bronchiectasis, and other conditions that may be complicated by emphysema should be treated.

Environmental Factors.—The many environmental factors that may irritate the tracheobronchial tree must be eliminated. This is particularly true if chronic cough and wheezing are present. A change in occupation may have to be considered if the patient is a farmer and if grain or barn dusts aggravate cough and dyspnea. This is also true of laborers exposed to industrial dusts, even though the content of the dust is not hazardous to normal persons. Tobacco smoke is one of the commonest respiratory irritants and must be avoided if the patient is to achieve the best chances of improvement. Numerous patients have attributed as much benefit to the discontinuance of smoking as to any other method of treatment. The relief of cough that may be achieved when smoking is stopped actually may remove one of the self-perpetuating factors of the emphysematous process. Voluntary suppression of nonproductive cough is of importance, since

many patients cough excessively. Cold, damp weather may aggravate dyspnea, and patients so affected should avoid undue exposure to inclement weather.

Medical Measures.—The various antibiotics are of invaluable aid in the treatment of patients who have chronic bronchopulmonary suppuration; these agents are of special benefit during the acute respiratory infections to which these patients appear unduly susceptible. The problems of acute respiratory acidosis may be avoided by prompt treatment of acute infections with the appropriate antibiotic. The constant use of a single antibiotic is not justified, however, because of the possibility of resistant organisms becoming predominant, allowing for perpetuation of chronic infection. Periodic culture of the sputum is important in guiding antibiotic therapy. The use of expectorants, such as iodides, to loosen tenacious secretions is frequently helpful.

The benefit of bronchodilators for patients who have emphysema has been known for many years. However, the use of epinephrine-like drugs has been limited mainly to asthmatic patients. The interest in the aerosolization of bronchodilating drugs has been revived with the advent of various types of positive-pressure breathing apparatus. The value of the continuous nebulization of 0.5 to 1 cc. of a solution containing a bronchodilator (for the 5 to 15 minutes needed to consume the dose) three or four times daily in the management of patients who have emphysema recently has gained wider clinical recognition. Isopropyl arterenol appears to be one of the most effective aerosolized bronchodilators. The beneficial results of such treatment have been attributed to the positive-pressure breathing apparatus that generates the aerosol and induces positive pressure during the inspiratory phase of respiration.[6] In the experience of my colleagues and me,[7] the nebulization of a similar dose of bronchodilating drug without intermittent positive pressure gives essentially the same objective and subjective response after a single application and after several weeks of systematic controlled treatment. Whether longer periods of combined treatment with the intermittent positive-pressure breathing apparatus and nebulized bronchodilating drugs will prove more advantageous than use of the nebulized bronchodilators alone is a problem still to be answered. The detailed instruction of these patients in the regular use of a nebulizer with a bronchodilating drug, outlined in detail elsewhere,[7] appears to be a practical and relatively economic method of treatment in conjunction with some of the other methods considered herein.

Physical Methods.—One of the simplest and most widely applied methods of physical therapy for patients who have emphysema is the use of proper breathing exercises. The rationale for this method, as for the other physical methods of management, is to assist the depressed diaphragm to take a more nearly normal position during expiration so that more diaphragmatic excursion can take place. The usual position of the diaphragm in patients who have emphysema is that of full inspiration. Consequently, further inspiratory effort is not only useless but fatiguing. Instruction in these breathing exercises stresses use of the abdominal muscles in active, slow, steady expiration. This apparently is more efficient than are the gasping inspiratory efforts of the upper thoracic, pectoral, and cervical muscles, which appear only to augment the continuous state of inspiration and overinflation of the lungs. Barach and Beck[8] have emphasized the value of the head-down position in assisting patients to learn the breathing exercises. These exercises tend to decrease the functional residual air, which consists of the respiratory gases not expelled from the lung during a normal expiration.[9]

Various abdominal belts have been recommended to aid in elevation of the diaphragm.[10] Some patients have observed varying degrees of symptomatic relief when properly fitted with a belt; however, others report no benefit or too much discomfort from wearing such belts. Since many patients who have emphysema already have abdominal complaints, anorexia, and loss of weight, the pressure caused by an abdominal belt may have

an unfavorable effect on nutrition in some patients despite its benefits to respiration. Artificial pneumoperitoneum has been advocated as a treatment for emphysema on the same theoretic basis as use of the abdominal belt; conflicting reports have appeared regarding its efficacy.‡

Methods Currently Under Evaluation.—The induction of myxedema to decrease the resting requirements of oxygen of the patient is being tried in this country, although few reports have been published.§ Such treatment is generally confined appropriately to patients with far-advanced disease who have received almost all the many prescribed methods of treatment without adequate response. Fifteen such patients treated by induction of myxedema at the Mayo Clinic have been followed for as long as 20 months. Although some of the patients had definite but limited improvement in symptoms, an almost equal number had no significant improvement. No improvement in the results of ventilatory studies has been observed, although performance of standard exercise tests and the amount of arterial oxygen saturation improved in a few cases. This palliative and indirect method of treating advanced emphysema requires further evaluation.

One of the inhibitors of carbonic anhydrase, namely, acetazoleamide (Diamox), has been reported to be helpful in some cases of severe emphysema with respiratory acidosis.[15] The mechanism of its action other than as a diuretic has not been clear in those cases reported. The problem of controlling all therapeutic factors in the several clinical studies consisting of a few desperately ill patients can be readily understood. The clarification of the specific value of acetazoleamide in respiratory acidosis awaits further study.

Surgical excision of large localized emphysematous bullae in the presence of otherwise normal lungs has been of value in selected patients who had significant symptoms. The surgical treatment of diffuse emphysema[16] is still in the investigative stages, and its value has yet to be determined.

‡ References 11 and 12.

§ References 13 and 14.

RESPIRATORY ACIDOSIS (CARBON DIOXIDE NARCOSIS, OXYGEN POISONING)

Some patients who have advanced emphysema experience significant degrees of arterial oxygen desaturation and also may retain abnormal amounts of carbon dioxide. The administration of high concentrations of oxygen to these patients may result in decreased ventilation, further acute retention of carbon dioxide, increased acidosis, mental confusion, delirium, and even death. This chain of events occurs while the appearance of the patient's skin paradoxically improves from that of cyanosis to a relatively healthy-looking pink. Cohn and associates[17] reviewed the pertinent literature and reported their experiences in the management of this condition. They reported the most consistent results from use of frequently interrupted oxygen therapy and the energetic use of nebulized bronchodilators similar to that already described. They stressed the fact that no substitute exists for constant attention to the progress of critically ill patients by an alert medical and nursing staff. Mechanical respirators of various types may be beneficial in some cases. The use of drugs causing respiratory depression should be particularly avoided.[18]

COR PULMONALE

Cor pulmonale with congestive cardiac failure occurring in patients who have emphysema is found almost exclusively among those who have demonstrable transient or persistent hypoxemia. Of particular importance, therefore, is the use of methods to improve the reversible element of hypoxemia and pulmonary vascular hypertension. Vigorous treatment of the complicating respiratory infections that may precipitate hypoxemia may be lifesaving. Harvey and associates[19] have stressed that recurrence of congestive cardiac failure due to cor pulmonale can be prevented if the arterial oxygen saturation can be maintained within normal limits. They advised use of aerosolized bronchodilators with oxygen as a relatively simple and effective method of treating the reversible elements contributing to congestive cardiac failure. If polycythemia is present, judicious

venesection may be helpful. General measures used in congestive cardiac failure are restriction of salt, digitalization, and the discreet use of diuretics. The response to these general measures is usually not so dramatic in patients who have emphysema as it is in patients who have left ventricular failure.

SUMMARY AND CONCLUSION

The clinical diagnosis of early pulmonary emphysema may be difficult because of the absence of many of the generally accepted criteria. The physiologic alterations of expiratory slowing, increased functional residual capacity, and underventilation of large portions of the lung often may be demonstrated in the examining room by eliciting prolonged forced expiration, by evidence of decreased intensity of breath sounds, and by a failure of the amplitude of breath sounds to increase normally during hyperventilation.

The limited understanding of the early pathogenesis of emphysema limits the possibilities of its early diagnosis and treatment. Once all the classic findings are present, the process frequently is self-perpetuating. Several simple basic therapeutic measures may afford most patients symptomatic relief and possibly slow the progress of this chronic disorder. These include avoidance of respiratory irritants, use of expectorants for patients who have tenacious secretions, suppression of nonproductive cough, judicious use of antibiotics in the control of complicating infections, exercises to promote abdominal breathing, emphysema belts for selected patients, and the systematic use of aerosolized bronchodilating drugs. If these measures are not effective, more complicated procedures may be used, but their effectiveness in patients not responding to the simpler measures may be limited.

More intensive use of aerosolized bronchodilators, with limited amounts of oxygen, is in order when respiratory acidosis occurs. Respiratory infections, which frequently precipitate such acidosis, must be controlled promptly. Mechanical respirators, if used under close observation, may help provide the adequate ventilation that is so important in these critically ill patients.

Cor pulmonale appears usually after arterial hypoxemia develops. Therefore, in addition to the usual measures prescribed for congestive cardiac failure, use of oxygen-generated aerosolized bronchodilating drugs is of particular value.

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Current Methods of Diagnosis and Treatment of Asthma

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As long as the underlying mechanisms of asthma are not fully understood, differences of opinion in regard to diagnosis and therapy will continue to exist. At least two methods, however, have repeatedly failed and should be discarded. First, a festoon of pharmacological agents usually delays the etiological diagnosis and confounds therapeutics. Secondly, an unsympathetic approach to the patient can only lead to failure.

Too often a patient is seen with severe symptoms of asthma even though he is taking medication of such variety as to require a valise. Such drugs may include ephedrine, potassium iodide, epinephrine, aminophylline, barbiturates, meperidine (Demerol), vitamins, antibiotics, antihistamines, and even corticotropin and corticosteroids. With such a barrage one might anticipate obliteration of asthmatic symptoms, but such an injudicious combination fails.

Since asthma is a puzzling disease, certain unreasonable attitudes have developed. "Friends" and relatives are prone to regard the victim's symptoms as a shield against responsibility. Admitting house officers are reluctant to send a patient with asthma to the ward of a friendly colleague. Nurses, remembering former demands of such charges, fail to smile. Patients with asthma are frequently referred to the newly established physician. The medical student joins the parade, for he must learn quickly. In this atmosphere rational study and therapy can be fraught with obstacles.

The purpose of this paper is to present an approach to bronchial asthma which is both rational and practical.

DIAGNOSIS

Diagnosis of any disease should be based on knowledge of the anatomy, physiology, and pathology of the affected organs. Miller [1] has described in detail the anatomy of the bronchial tree and lungs, and Drinker [2] has outlined the important clinical points of respiratory physiology. Morphological changes in asthma are described in most textbooks of pathology. Because many cases of asthma are due to antigen-antibody reactions, certain principles of immunology must be understood. Raffel [3] has summarized the pertinent principles.

Asthma has been considered to be one of the psychosomatic diseases. There appears to be little reason to doubt that mental attitude toward asthma is important, as this attitude

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is important in every disease. The question whether a few or many cases of asthma are due to deep-seated emotional factors, with an onset in infancy or childhood, remains unanswered to date, but the possibility of such factors deserves attention.

All asthma falls into one of two broad classifications: asthma of known etiology or asthma of undetermined etiology. Repeated attempts to find the responsible antigens must be made, because asthma of undetermined etiology can only be treated symptomatically.

The most important tool in the diagnosis of asthma is history. To skim over this is erroneous. Rackemann [4] outlined the phases of this history. If possible, the exact date of the first attack should be pinpointed to month, day, and year. This date should be correlated with locality, age, and occupation of the patient, his pets, diet, household furniture, and emotional status. The duration and severity of this first attack is important. Equally important are the history of subsequent attacks and his condition between attacks. Previous or present allergic diseases such as eczema must be considered. The family history of allergic disorders must be thorough and should include allergic histories of ancestors, contemporaries, and offspring. Previous and present therapy as well as results should be scrutinized and recorded. A thorough systemic review may yield additional clues. Such a history may require several sessions, each of an hour's duration, but it may well save years of anxiety, illness, and blundering.

A complete physical examination is indicated. Nasal polyps or a pale boggy nasal mucosa will be missed if the nose is not examined. Unilateral wheezing points to a foreign body, tumor, or infectious process. Nocturnal wheezing in a patient with an enlarged heart with murmurs and with peripheral edema suggests cardiac disease rather than bronchial asthma.

Roentgenography is useful. Roentgenograms of the sinuses may locate polyps or infection, and those of the chest can determine heart size and the presence of foreign bodies, tumors, or infections. Fluoroscopy provides data concerning movement of the diaphragm and mediastinum.

Discreet skin testing is an aid in diagnosis. Any patient may theoretically be sensitive to countless antigens. If the history is thorough, rarely does the indicated number of skin tests exceed two figures. To prevent general systemic reactions, scratch tests should precede intradermal tests. Skin tests of inhalants are more reliable than are those to foods. Skin tests should be correlated with the history. A patient in New England with asthma from mid-August to frost is usually sensitive to ragweed. If a skin test to this antigen happens to be negative, the history usually proves correct. If a patient never has had asthma during the ragweed season, it is unlikely that ragweed is a factor even if his skin test to ragweed is positive. If a patient has never eaten a food, skin testing him for it is of no practical value. A New England child was recently told not to eat barracuda, as his skin test to it was positive. The child had never eaten barracuda, and his chances of exposure seem minimal. Skin tests are useful, but they can mislead if followed with abandon.

TREATMENT

When the control of asthmatic symptoms is not the major problem, the attempt to establish an etiological diagnosis should be undertaken without delay. Frequently the paths of the physician and patient first intersect when the patient has severe symptoms of asthma. Symptomatic therapy is essential, but a short history, emphasizing onset, medication, and results to date, is necessary. A thorough physical examination is mandatory.

Symptomatic Therapy

Certain concepts of therapy are worthy of comment. The physician must appear sympathetic, calm, and interested at all times. Whether the patient is to be treated at home or hospitalized, he should be placed in a quiet well-ventilated room. Patients in the midst of a severe prolonged attack already refractory to several drugs should be sent to the hospital. This also applies to those who are

living in an environment full of probable antigens. Having determined recently administered medications and their results, the physician should discontinue drugs which have currently failed to provide relief when given in proper dosage as well as those which have caused untoward side-effects in the past. Such a step avoids a multiplicity of medications, which is likely to do more harm than good.

In acute asthma bronchospasm, which can be relieved by several drugs, is usually present. The agent of choice is subcutaneous epinephrine 1 : 1000. Frequent injections of 0.3 to 0.5 ml. spaced at intervals of 20 minutes are more effective than one large dose. Success may be determined only after an hour. If epinephrine proves effective, the patient is instructed in its subcutaneous use or taught to inhale nebulized epinephrine 1 : 100. If the patient has concomitant hypertension, isoproterenol (Isuprel) hydrochloride 1 : 200 may be substituted for epinephrine by inhalation. In some patients epinephrine will fail. A few patients, after initial success, may become refractory. In both groups epinephrine should be discontinued, but often after an interval of 24 hours or longer epinephrine should be tried once again in those patients who become epinephrine-fast.

A less potent antispasmodic but more sustained in action is ephedrine. It has been used with varying success to control mild attacks of asthma that tend to recur. There is the occasional patient who has regular attacks during the night and can obtain a full night's rest with a dose at bedtime. The side-effects of palpation and tenseness frequently accompanying use of ephedrine make it a poor risk, in anxious, intent patients.

Aminophylline is an efficient bronchodilator. In addition, it reduces edema of the bronchial mucosa. It is most effective by slow intravenous injection, quite effective by rectum, and least so by mouth. Nausea and vomiting may force interruption of aminophylline therapy.

In patients with asthma, thick mucus filling the lumina of bronchi and bronchioles can lead to death. To liquefy such mucus, expectorants have been tried for many years. Iodides [5] appear to be the best available agents. Potassium iodide can be given orally, and sodium iodide has been prepared for intravenous use. Rasmussen [6] has reported two patients in whom iodide sensitivity may have caused polyarteritis. If untoward symptoms develop while the patient is on iodides, such medication must be discontinued.

Many patients are apprehensive and tense during an attack of asthma. In such persons sedation is often desirable, but it can be dangerous, especially when the attack of asthma has been severe and prolonged. Chloral hydrate is the drug recommended, as it has the least effect on the respiratory center. Morphine is contraindicated. Meperidine hydrochloride is not used by us, for it does depress the respiratory center and can cause addiction. A recent report [7] showed an increased addiction to it. Twenty-five of the four hundred fifty-seven addicts to meperidine took it to control asthma. Within recent months two such patients have been seen at the Massachusetts General Hospital. Avoidance of barbiturates is urged, because patients with chronic asthma develop a tolerance to them and because some show undesirable side-reactions.

The antihistamines have been used extensively in asthma, but they have proved ineffective. Their mild sedative effect, particularly in children, has proved valuable. Theoretically the antihistamines [8] act by occupying the receptors of cells where histamine would have to attach to produce symptoms.

Asthmatic patients often become dehydrated, and they should receive required fluids by an appropriate intravenous infusion. To this infusion may be added epinephrine, aminophylline, or sodium iodide if such drugs are indicated.

Oxygen is justified only in patients having a lowered oxygen saturation of arterial blood. Those patients with emphysema [9] and some with chronic asthma [10] have a high tolerance to carbon dioxide. Respiratory stimulus, therefore, depends on oxygen lack. In these

patients oxygen therapy is dangerous, for respiratory movements may cease when oxygen lack is compensated. Schiller and Lowell [11] found that mixtures of oxygen and helium have no advantage over oxygen alone. Oxygen tents are contraindicated in patients frightened by confinement. The nasal catheter is more suitable.

Corticotropin, cortisone, hydrocortisone, and, recently, prednisolone and prednisone (metacortandralone and metacortandracin) have been available for suppression of asthmatic symptoms. All are effective, but each has side-reactions. The modes of action of these hormones are not understood, but they can relieve all symptoms and signs of asthma.

Neither corticotropin nor the adrenocortical steroids have been available long enough to set up fast rules, but for the welfare of patients certain generalities must be considered. These agents must not be used in patients with mild asthma but should be reserved for patients with very severe asthma. Even these patients should not be subjected to these hormones until treatment such as that previously outlined has failed. Ideally, each patient with asthma severe enough to warrant the use of these hormones should be in the hospital for initial therapy. Corticotropin appears to have no advantages and at least two disadvantages in relation to cortisone or hydrocortisone. Commercially available corticotropin preparations contain some foreign protein, and the possibility of allergic reactions exists. Such allergic reactions have been reported.* In addition, corticotropin must be given by injection. Cortisone and hydrocortisone are now the agents of choice. Contraindications, complications, and dosage schedules have been presented in detail.† Prednisone and prednisolone have only been available a few months. They are effective in lower doses than cortisone or hydrocortisone, but side-effects [18] have already been reported. More study is required before they can be adequately compared with either cortisone or hydrocortisone.

* References 12 and 13.

† References 14-17.

Definitive Treatment

Every attempt to make an etiological diagnosis must be made, once symptoms are under control. After the diagnosis is established, several modes of positive therapy are available.

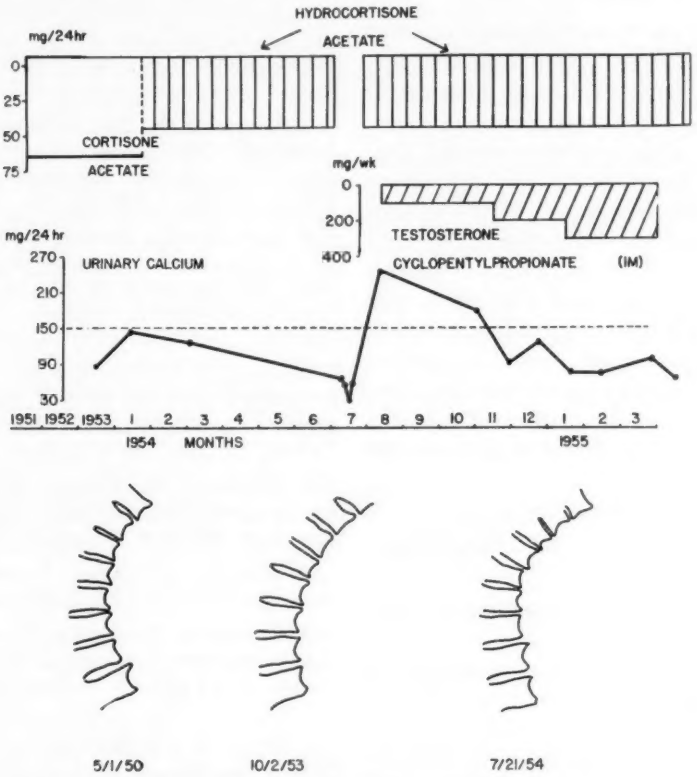
If asthma is based on the reaction of antigens and specific antibodies, the best treatment is to separate the patient from the offending antigens. For example, the cat or dog can be removed permanently. Then the problem is solved. In pollen asthma, the patient may move to an area free of offending pollens or live in rooms equipped with filtering devices. Obviously such solutions are not always practical. Hyposensitization to offending antigens then should be given a reasonable trial.

In some patients, no demonstrable antigens appear to exist and emotional factors may seem important. Here, every physician can help by being sympathetic and attentive. In some, deep-rooted problems are best handled by an understanding psychiatrist. The attending physician should aid the psychiatrist by directing medicinal therapy.

A small group of patients develop severe, perennial asthma. Repeated attempts to make an etiological diagnosis fail. Psychiatry is frequently tried and proved wanting. These patients often become refractory to symptomatic treatment and become invalids. Many can be relieved by the adrenocortical steroids and maintained symptom-free on daily doses for years. Initially, enough of the chosen steroids should be given to suppress symptoms completely. The daily maintenance dose is found by lowering the daily dose until symptoms begin to reappear. The optimal daily dose is the lowest on which the patient is free from symptoms and is a few milligrams above the dose on which symptoms reappear. Patients have been maintained symptom-free over four years and have been reported in detail.‡ Complications have been encountered. The most serious is osteoporosis with compressed fractures of vertebrae. Attempts to control

‡ References 14 and 15.

developing osteoporosis with either ethinyl estradiol or testosterone are under way, but final evaluation must wait. It is of interest that some patients on rather high daily doses of steroid do not appear to be developing excess excretion of calcium in their urine, even though they have not received either estrogenic or androgenic substances. Women who have had an artificial menopause because of removal of both ovaries are especially susceptible to osteoporosis.



Summary of course of male asthmatic patient reported in text.

To illustrate a method of approach and control of maintenance steroid therapy, the following case is presented. The Figure outlines the course.

REPORT OF CASE

The patient's first asthma appeared at age 59, in May, 1941. Asthma was persistent from onset. Epinephrine 1:1000 subcutaneously provided adequate relief for one year. Frequent hospitalizations and a prolonged visit in Arizona failed to help. On April 30, 1951, he was admitted to the Massachusetts General Hospital with severe asthma. Careful studies failed to disclose responsible antigens. Conservative therapy did not help. Physical examination showed weight 153 lb., B. P. 160/90, polypoid degeneration of nasal mucosa, inspiratory and expiratory wheezes, bradycardia. Laboratory studies showed venous pressure 110 mm. saline; vital capacity in three seconds, 2.2 liter. Roentgenograms showed periodontoclasia, slight thickening of membranes of antra, emphysematous chest, and slight osteoporosis of thoracic and lumbar vertebrae. He was placed on cortisone. After four days (700 mg.) the asthma was cleared. Within a week the patient was discharged free of asthma. Until Oct. 31, 1953, he was maintained symptom-free on an average daily dose of 70 mg. of cortisone. Since then he has been on hydrocortisone, with an average daily maintenance dose of 50 mg.

At first, his 24-hour urinary excretion of calcium was not above 150 mg., but in July, 1954, it became high. At this time roentgenograms showed progressive osteoporosis and compressed fractures of

thoracic vertebrae. On testosterone his 24-hour urinary calcium excretion has fallen below 150 mg. To date he has had, fortunately, no symptoms from his fractured vertebrae.

On cortisone, at age 73, he works daily. He is on a moderately low-sodium diet (1 gm.) daily. He has developed a serious complication, but the last four years of his life have been asthma-free and productive. Hydrocortisone was withdrawn in July, 1954, but severe asthma soon necessitated return to steroid treatment.

COMMENT

Asthma can be treated successfully. Most patients can be cured by removal of offending antigens, once an etiological diagnosis is made. A few receive aid from psychiatry. Etiology can not always be determined. Frequently simple medication like epinephrine suffices. A few require one of the corticosteroids to prevent invalidism. Long-term maintenance steroid therapy remains hazardous and requires cooperation of patient and physician. Such therapy must be justified in each patient individually. Since the adrenocortical steroids are effective and since they may cause serious side-reactions, the importance of making an etiological diagnosis has increased.

SUMMARY

A method of diagnosis of asthma is outlined.

The importance of an etiological diagnosis is stressed.

One rational approach to treatment of asthma is presented.

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Some Current Concepts of Pulmonary Edema

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It appears that pulmonary edema would be a subject about which much agreement could be reached as to its definition, physiopathology, clinical recognition, and treatment. However, such is not the case. There exists today a marked dichotomy of thought between clinicians who study patients and physiologists who study mechanisms. The internist usually designates the condition by a physiologic term, namely, "left ventricular failure," which physiologists abhor. On the other hand, the physiologists adhere to a simple clinical term, "acute pulmonary edema."

It is with the above in mind, and with the realization that as clinicians it behooves us to think therapeutically as well as physiologically, that the following report is presented. It is not intended to be an extensive review of the literature but simply a review of some of the more recent findings as related to therapy.

DEFINITION

Pulmonary edema may be defined as the transudation of plasma into the alveoli and its extension by air currents into the passages of the respiratory tract.

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PHYSIOPATHOLOGY

The basic factors that are involved in pulmonary edema are the following as they affect the pulmonary capillary: (*a*) the hydrostatic pressure; (*b*) intrathoracic pressure; (*c*) protein osmotic pressure; (*d*) capillary permeability; (*e*) lymphatic "run off."

The normal hydrostatic pressure in the pulmonary capillary is approximately 10 mm. of mercury. This would tend to transude the fluid in the capillary into the loose lung tissue surrounding it. However, the plasma traversing the lung capillaries has about 7% protein, which produces an effective colloid osmotic pressure amounting to 25 or 30 mm. of mercury. This osmotic pressure exerts a stronger force to retain fluid in the pulmonary blood vessels. However, this retention force is somewhat lessened by the negative intrathoracic pressure (—5 to —10 mm. of mercury, normally) which is exerted on the capillary walls.

A rise in capillary pressure above the colloid osmotic pressure can result if the resistance to the outflow of blood from the lungs is increased, as it is in obstruction to the pulmonary veins or in pure mitral stenosis or in left ventricular failure. In these conditions, blood pumped by the right ventricle would tend to accumulate behind the obstruction. Since the systemic blood volume is relatively large and the potential volume of the pulmonary vascular system relatively small, the additional blood forced into the latter will either increase the tension on the vessel walls or distend the vessels or both and thus cause the pressure in the pulmonary veins as well as in the arteries to rise. Pulmonary edema would develop readily, since intracapillary pressure is also elevated.

It has been argued that the simple increase of pulmonary capillary pressure is not the

prime factor in the causation of pulmonary edema. This has been suggested because pulmonary edema is not often associated with mitral stenosis, even in instances of high pulmonary artery pressures. It is our belief that these occurrences are explainable. In a previous study [1] on the hemodynamics of mitral stenosis, we found some interesting data in relation to pulmonary vascular resistance. The data reported emphasized the importance of the role of the absolute intraluminal pressure in total resistance in the normal pulmonary vascular bed. It is important to mention that resistance within a blood vessel can be indexed by a hemodynamic formula, i. e., resistance equals pulmonary pressure gradient divided by the cardiac output. Since blood vessels are distensible, elastic structures, the intraluminal pressure must be an important determinant of the vessel diameter. Since the volume flow for a given pressure gradient varies with the fourth power of the radius of a tube, it is obvious that this factor can be of great importance. Thus, it is possible to increase the pulmonary vein pressure with a resultant increase in the cross sectional area of the pulmonary vascular bed, and, therefore, the movement of a given volume of blood is accomplished with a smaller pressure drop. As a matter of fact, Riley [2] found a decrease in the pulmonary artery pressure when a normal subject exercised.

In mitral stenosis one ordinarily finds elevations in pulmonary artery pressure when the disease is advanced and of long duration. It is in those instances that marked organic changes occur in the pulmonary arteriole, raising the pulmonary artery pressure but actually protecting the pulmonary capillary at rest.

A rise in capillary pressure above the colloid oncotic pressure can also occur when the right ventricular output is great enough in a given period of time to exceed the run-off capacity of the pulmonary venous tree. Sudden, rapid hypervolemia from overloading the systemic return to the right heart is an example and can cause pulmonary edema if the reserve of the left ventricle is reduced. It can also occur under conditions of hypoproteinemia or when hemodilution with saline is induced.[3]

Since a membrane is involved in pulmonary edema (capillary membrane), changes in its permeability may occur. Just what initiates these changes is still unknown. It is possible that when the output of the ventricle drops below a certain critical level certain hormonal changes in the adrenals, kidneys, etc., take place. These, in turn, may affect the permeability of various capillary membranes. On the other hand, specific changes in the pulmonary capillary membrane permeability have been claimed for certain noxious compounds. Thus, when air containing 10% oxygen was administered Drinker [4] claimed that the permeability of the membranes was increased. Liljestrand [5] reported that, under similar conditions, the moderate anoxia so produced caused pulmonary hypertension. The pressure rise in the pulmonary artery appeared to be independent of the increase in blood flow, the increased left atrial pressure, or the nervous control of the vessels.

With regard to alterations in intrathoracic pressure as a cause of pulmonary edema, Drinker [4] demonstrated that stimulation of respiration by inhalation of carbon dioxide produces a marked increase in lymph flow from the lungs of the dog. He interpreted the experiments as indicating evidence of augmented filtration from the lung capillaries, induced by changes of intrathoracic pressure as a result of the violent breathing.

Recently a neurogenic factor in pulmonary edema has been proposed.[6] This has been proposed because of the frequent association of pulmonary edema with cranial trauma, cerebral hemorrhage,[7] encephalitis, and even spinal cord lesions. Cushing,[8] many years ago, published his well-known work relating cerebral compression and systemic arterial hypertension. This work was affirmed by various workers in later years. When pulmonary edema did occur in association with these lesions, it was thought to result from an increase in pulmonary capillary permeability mediated by nerve impulses,

independent of that hemodynamic change which might readily be expected to produce pulmonary edema, namely, an increase in pulmonary capillary pressure.

More recent investigators * have shown that in reality one should designate it as a neurohemodynamic effect rather than a pure neurogenic effect. Nervous influences that cause pulmonary edema must act by so changing the peripheral and central blood volumes that, when a shift of blood occurs, it must be shifted to a vascular bed with little or no constrictor potential, namely, the lung. This can be accomplished by a variety of means. Bradycardia and lowered cardiac output, peripheral hypertension occurring simultaneously with an already damaged heart, and constriction of the pulmonary venule outflow tract are some of the hemodynamic changes that can occur. Each can lead to a change in the effective transcapillary filtration pressure.

It would appear that the mechanism of pulmonary edema could be explained by factors which would allow for unbalanced pressure differentials to occur and therefore result in fluid movements into the alveolar and extracellular spaces.

CLINICAL PICTURE

The clinical picture of pulmonary edema has been well described and need not be discussed at this time.

TREATMENT

Pulmonary edema when not adequately treated kills because of uncorrected anoxic anoxia and hypercapnia. Every effort toward the prevention of pulmonary edema should be made. The patient who seems likely to go into pulmonary edema should be affected favorably by rest, digitalis, diuretics, salt balance, water regulation, and sedation.

Granted that a patient is properly prepared and must undergo surgery, it is wise to add the antibiotic preoperatively. In the presence of congestion, susceptibility to pulmonary and other infections is increased. During surgery, every effort must be made to maintain a clear airway. As has been mentioned earlier, an obstructed airway will augment the negative intrathoracic pressure and result in pulmonary edema. Blood loss must be accurately replaced so that overtransfusion, with rapid hypervolemia, does not result. The use of weighing scales in the operating rooms to determine blood loss is a useful adjunct to prevent overtransfusion. Saline and other fluids should be administered with caution during operation and in the postoperative period. As a matter of fact, it is best to be on the safe side and administer less than the so-called required amount of fluids to the patient who seems a likely candidate for pulmonary edema. More patients, in our estimation, are killed by overhydration than by underhydration. Another useful point is to elevate the head of such a patient in the postoperative period and to administer well-hydrated oxygen via a nasal catheter. Constant attention to bronchial toiletry is also important. These patients should be encouraged to cough and move about in the postoperative period. Prevention of abdominal distention will, of course, aid in the prevention of pulmonary edema by allowing for greater ventilatory movements of the diaphragm and mitigating abnormalities in the abdominothoracic venous pressure gradient.

We should like to mention at this time that we have purposely avoided the discussion of pulmonary edema as part of the picture of congestive heart failure. Knowledge of the mechanism of congestive heart failure is still incomplete. Certainly the hemodynamic mechanism is not the only one. There is nothing to prevent the development of attacks of acute pulmonary edema in patients with chronic congestive failure. It is common to see the two together—the pulmonary syndrome develops as the chronic disorder worsens and disappears as the chronic failure improves. It is clear that, under these circumstances, the treatment of the two syndromes is essentially the treat-

* References 9 and 10.

ment of the primary disorder. However, in the treatment of attacks of pulmonary edema per se, whether isolated or associated with chronic myocardial insufficiency, there are some useful therapeutic adjuncts.

Once pulmonary edema is present, immediate treatment should be instituted. Oxygen should be administered, as it serves the obvious purpose of facilitating correction of the generalized anoxia that results from pulmonary edema. From the previous discussion, oxygen tends to diminish the edema itself, since anoxia increases the amount of transudation from the blood vessels of the lungs. We have been particularly impressed with the use of oxygen given under positive pressure breathing with a Bennett valve. Intermittent positive-pressure breathing [11] tends to diminish the volume of blood entering the right heart and, therefore, the lungs. It also tends to widen the bronchial pathways. Recently Luisada [12] has added alcohol vapor to the intermittent positive-pressure breathing and has found it beneficial because of its antifoaming action. We have also found it useful.

Morphine alone will alleviate a large number of attacks. It can be administered intravenously. Caution is advised in the elderly patient and in those with pulmonary emphysema. Morphine acts by alleviating the labored breathing and concomitant decrease in intrathoracic pressure which tends to increase pulmonary edema.

Digitalization, of course, is obvious. The rapid acting glycosides are most frequently used.

From a clinical standpoint, bloodless phlebotomy (tourniquets) and phlebotomy are the most direct means of producing a decrease of the inflow load in the right heart.[13] These measures will allow for an increase in vital capacity and occasionally lead to an increase in the arterial blood saturation. The cerebrospinal fluid pressure falls after venesection, a factor that in itself may tend to relieve dyspnea. However, it should be borne in mind that all these favorable actions must be balanced against the possibility that shock may be precipitated by venesection, with a resultant lowering of cardiac output.

Aminophylline given intravenously or by suppository has definite clinical value. The drug is apparently a powerful relaxant of smooth muscle, and, therefore, the element of bronchospasm is relieved. It must be noted that aminophylline has a powerful action on the smooth muscle of blood vessels if given rapidly. This action should be avoided, with the bronchodilator action still obtained by the slow administration of the drug.

As mentioned before, the treatment of pulmonary edema associated with chronic congestive heart failure is the treatment of the latter disease. At this time, a discussion of such treatment is not necessary.

Finally, strong mention should be made of two very useful procedures: (1) atropinization, and (2) tracheotomy. Since it has been shown that the parasympathetic pathways are involved in pulmonary edema of neurogenic origin (brain trauma, etc.), it became obvious that atropine administration might be of benefit. Experimentally this has been the case,[9] and atropine in patients may allow for a period of grace during which pulmonary edema is prevented and operative intervention relieves the rising intracranial pressure.

In the unconscious and semicomatose patient or the patient with extensive fluid in the bronchial tree, one of the finest adjuncts in the treatment of these patients is tracheotomy. We have found it to be so effective that our policy has been that, when tracheotomy is considered, it should be done immediately. We have not been sorry in any instance. Tracheotomy accomplishes many things in these patients. It by-passes the vocal cords, which may be paralyzed and add to decreased intrathoracic pressure. It decreases the respiratory dead space of the mouth and pharynx. It allows for a direct passageway into the bronchial tree so that fluid can be suctioned out by a physician or a nurse. It allows for positive-pressure breathing, if necessary.

It is our opinion that in severe instances of acute pulmonary edema tracheotomy will achieve a much wider range of usefulness in the future than it has in the past.

SUMMARY

A concept of the mechanism of pulmonary edema is presented. Pulmonary edema, in all probability, is primarily the result of increased effective filtration pressure. When it is part of the picture of congestive heart failure, other factors must be considered and the treatment must be of congestive heart failure.

The treatment of pulmonary edema is discussed. It can and should be physiologic. Tracheotomy as an adjunct in the treatment is suggested.

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Thrombophlebitis Migrans and Visceral Carcinoma

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Many clinicians have had occasion to observe that patients who have carcinoma involving an internal organ are prone to develop thrombophlebitis in one or more superficial veins. Trousseau * first wrote about this observation 94 years ago. In brief, he stated that, if the diagnosis of a suspected carcinoma of an internal organ could not be verified, the sudden and spontaneous appearance of thrombophlebitis in a larger vein afforded necessary proof for diagnosis. Trousseau's basic observation stands, but in the light of our present knowledge certain other facts may be added to his statement. For example, the appearance of one or more lesions of thrombophlebitis may be the first tangible evidence of the presence of a visceral carcinoma. It is, therefore, the obligation of the clinician to classify as accurately and as early as possible any type of thrombotic lesion encountered.

There are two types of thrombotic lesions which are carcinogenetic in origin. These are basically and otherwise closely related, but they are distinctive in their objective characteristics and in their reactions in local tissues. One type is indistinguishable from the histologically classical variety of thrombophlebitis; the other, more characteristic, type we speak of as thrombophlebitis migrans.

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From the Division of General Medicine, Department of Medicine, Henry Ford Hospital.

This paper was discussed by Dr. J. Earl Estes Jr., of Rochester, Minn., and by Dr. William T. Foley, of New York.

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* Trousseau, A., cited by Thompson.[1]

CHARACTERISTICS OF THE CLASSICAL THROMBOTIC PROCESS WHICH OCCURS WITH CARCINOMA

Since thrombophlebitis migrans may be considered to be a variant of the ordinary thrombotic process, the carcinogenetic aspects and relationships of these ordinary thrombi will first be reviewed. Much of the factual data concerning the occurrence of a single thrombus or of multiple thrombi in association with carcinoma, especially in the body or tail of the pancreas, was revealed in Sproul's publication in 1938.[2] Kenney, in 1943, published his observation from a detailed study of vascular lesions which were associated with 51 cases of carcinoma of the pancreas.[3] Both of these statistical studies emphasized anew the importance of considering the presence of multiple thrombi as a diagnostic criterion in suspected cases of carcinoma of an internal organ, more particularly in carcinoma involving the body or the tail of the pancreas. These autopsy records show the incidence of a single thrombus to be as high as 56% and the incidence of multiple thrombi 30% to 33% in patients with carcinoma involving the body or tail of the pancreas.

The frequency with which such thrombi may be recognized clinically in carcinoma is evident in a report by Elman and Wheat.[4] These authors found that the presence of the ordinary type of multiple thrombi permitted an early preoperative diagnosis in 22% of 157 collected cases of carcinoma of the pancreas. This discrepancy between clinical and pathological incidence is understandable, since some of the single thromboses are atypical and minimal in degree and their significance may not at first be appreciated.

I refer, for example, to the frequency of small, localized areas of thrombosis which occur at the sites of venipuncture in patients with carcinoma of either the stomach or the pancreas.

These single or multiple thrombi have no unusual characteristics to indicate that they are carcinogenetic in origin. The presence of carcinoma may be suspected, but the diagnosis must be confirmed through other investigations.

CHARACTERISTICS OF THROMBOPHLEBITIS MIGRANS

Fortunately, the lesions of thrombophlebitis migrans seem for the most part to be more uniformly characteristic and are more easily recognized as such. These vascular lesions are usually multiple. Eighty per cent occur in male patients beyond the age of 35 years. They may occur as a related group in a limited body area, but the lesions are more likely to be widely scattered and involve any part of the body or extremities. Each individual lesion affects only a short segment of the veins. The lesions are usually reddened and intensely inflamed and tender and are frequently fulminant. Their most significant characteristic is that they appear, gradually subside within two or more weeks, and within a similar period may recur along the course of the same or neighboring veins. Fever and leucocytosis are generally a conspicuous part of each flare-up. Although the obvious lesions are evident only in superficial veins, the involvement of deeper veins, including those of various viscera and of the mesentery, may occur. Sullivan and Walske [5] state that at autopsy it was found that 5 of 13 cases had extensive involvement of mesenteric vessels. Panthrombophlebitis may occasionally be observed.

Another unusual characteristic of thrombophlebitis migrans is the concurrent development in its later stage of nonbacterial, fibrinous vegetations on heart valves. These vegetations commonly give rise to superficial arterial emboli or pulmonary emboli. Thus, the same patient may exhibit numerous lesions of thrombophlebitis migrans and, coincidentally, also show evidence of multiple embolic phenomena.[14] When these two conditions are both present, the diagnosis of visceral carcinoma may be made, almost without question.

In fact, as a working hypothesis, the presence of a single, spontaneous thrombophlebitic lesion must be regarded with suspicion until its status is proved; multiple thrombophlebitic lesions strongly suggest the presence of visceral carcinoma, especially of the pancreas, and the presence of typical lesions of thrombophlebitis migrans may, with rare exceptions, be regarded as being pathognomonic of visceral carcinoma. It is nowise clear why the altered biochemical mechanism should on one occasion produce but a single evident lesion of thrombophlebitis, in another instance multiple thrombi, and in still another the quite different type of thrombotic manifestations of thrombophlebitis migrans.

Both the single and the multiple types of these carcinogenetic thrombi may need to be differentiated from so-called idiopathic thrombophlebitis. This latter type has been observed to occur intermittently for years without the development of carcinoma. There is seldom any difficulty in differentiating other thrombotic lesions from the classical lesions of thrombophlebitis migrans.

FREQUENCY OF OCCURRENCE OF THROMBOPHLEBITIS MIGRANS

The significance of these thrombophlebitic lesions is not always fully appreciated. Inquiry made at a few clinics indicated an extreme paucity of such cases. Actually, the phenomenon is not a rare one by any means; at least Wright and his co-workers [6] were able to confirm the diagnosis of carcinoma in 20 patients in whom the disease process was not suspected until the lesions of multiple thrombi or thrombophlebitis migrans suggested the presence of visceral carcinoma.

HISTOLOGICAL AND INFECTIOUS FACTORS

Various reports concerning the histological changes of the vein wall indicate that there are no significant local inflammatory changes accompanying the ordinary type of multiple

thrombi. Kenney's studies of autopsy findings in 30 cases showed no unusual reaction within the vein walls. Cultures from the vein and thrombus are usually negative. Barker made cultures in 11 cases, all of which were negative.[7] Blood cultures are usually negative also.[9] Only rarely have tumor cells been found to have invaded the area of the thrombophlebitis.† These reports apparently refer in most instances to the type of multiple thrombi associated with carcinoma. Detailed histological reports are lacking concerning the reddened, inflamed, and exquisitely tender lesions of thrombophlebitis migrans in their different stages.

COAGULATION FACTORS

The usually measured factors in coagulation, such as the sedimentation rate, thrombocytes, bleeding and clotting time, plasma fibrinogen, prothrombin time, and studies of hepatic function, are not sufficiently deranged to be a causal factor in the thrombophlebitis. Speculative theories about platelet adhesiveness and the effect of thrombocytosin are as yet unproved.[8] There is, however, a marked reduction in the thrombosing tendency in the presence of jaundice, as would normally be expected.[2]

TIME OF APPEARANCE OF LESIONS OF CARCINOGENETIC THROMBOPHLEBITIS

The significance of these vascular lesions assumes an added importance with a proper appreciation that they may at times serve as a criterion in the early diagnosis of carcinoma. Not infrequently, at the time the thrombophlebitis is observed there may be no other signs or symptoms to suggest the presence of carcinoma. In certain cases, the migrating thrombophlebitis may not appear until the terminal weeks of the patient's illness; however, it is not uncommon for the ordinary thrombotic lesions to be observed several months or even a year before the carcinoma would otherwise be diagnosed.[9] It has, in fact, been repeatedly emphasized that in a certain number of cases confirmatory evidence of the presence of an obscure visceral carcinoma may not finally be proved except by operation or autopsy.

LOCALIZATION OF LESIONS OF THROMBOPHLEBITIS MIGRANS

There is no certain or fixed pattern of localization of these lesions. They occur in previously healthy veins, and, as a rule, one extremity or more may be involved. The lesions rarely occur in varicosities of the lower extremities or around the site of varicose ulcers. Occasionally, when a sufficient number or all of the lesions are closely grouped together, this localization may indicate that the carcinoma has originated in a nearby locus. For example, a bronchogenic carcinoma with extension to the upper mediastinum may be accompanied by multiple areas of thrombophlebitis in veins of the neck, shoulder area, and upper lateral chest wall. Far more frequently the lesions of thrombophlebitis migrans are widespread and involve the extremities in particular.

VISCERA INVOLVED IN CARCINOMA

In an earlier period it was thought that thrombophlebitis migrans was limited to cases of carcinoma originating only in the pancreas. It is true that by far the greatest number of cases has been reported to occur when carcinoma involved the body or tail of the pancreas. Rather strangely, multiple thrombi occur infrequently when the carcinoma involves the head of the pancreas. Sproul[2] found only three such cases, or 9.7%; Kenney found none in his series.[3] Gradually accumulated data indicate that the malignant lesion may, in lesser frequency, be primary in any viscera. Thrombophlebitis migrans has also been observed to occur in cancer involving the liver, lungs, stomach, gall bladder, and, more rarely, the urinary bladder, ovary, rectum, and uterus and in clinically silent leukemia.

The degree of specificity of the influence of carcinoma cells upon thrombus formation will be evident in the ensuing points to be reviewed.

† References 2 and 6.

TYPES OF CARCINOMA ASSOCIATED WITH MULTIPLE THROMBI

Thrombophlebitis migrans as a tissue response has not been observed in nonmalignant tumors, even in nonmalignant tumors of the pancreas. Studies of 25 cases which involved benign epithelial tumors which arose in the pancreas revealed the presence of a single thrombus formation in only 9 instances, and no case showed multiple thrombi [2]; also, in 83 reported instances of metastases to the pancreas there was no single instance of multiple thrombi [2]; however, other opinions differ on this point. It seems significant also that the presence of multiple thrombi is said to be quite rare in patients with sarcoma and that the lesions of thrombophlebitis migrans are reported not to occur in association with this type of tumor.

There is considerable evidence to suggest that the phenomenon of multiple thrombi occurs exclusively within the group of mucinous carcinomata.‡ It has been pointed out that in all cases of carcinoma of the body or tail of the pancreas in which multiple thrombi are found the tumor was of the mucinous type. In 13 cases observed by Sproul, all except 1 patient with multiple thrombi had mucinous foci in the primary tumor; only 3 of the 13 cases showed mucin and no thrombi. To what extent these observations apply to those cases of carcinoma which exhibit the lesions of thrombophlebitis migrans is as yet not entirely clear. It is certainly not difficult to prove that tissues such as the prostate, which are seldom the source of a mucus-producing carcinoma, have, correspondingly, an exceedingly low incidence of thrombophlebitis migrans. Thus far, the causal relationship of mucus-producing carcinomata and the action of mucolytic enzymes as a factor in producing thrombophlebitis or thrombophlebitis migrans have not been adequately explored or explained.

THE DEGREE OF MALIGNANCY DETERMINES THE FREQUENCY OF THROMBOPHLEBITIS

The frequency of the occurrence of multiple thrombi is reported to be greater as the gradient of the malignancy increases; in other words, the incidence both of venous thrombosis and of metastases was greater with the increase in the grade of malignancy.[11] One can but speculate whether the same factor which determines the more rapid growth and invasiveness of the carcinoma also determines the frequency of the occurrence of multiple venous thrombi; at least it may be said that there is apparently a quantitative factor, acting directly or indirectly, in the production of multiple thrombi.

Another interesting relationship has been pointed out in the reported cessation of the occurrence of multiple thrombophlebitis after surgical removal of the original or primary site of carcinoma.[6] This observation further suggests a direct carcinogenetic effect in the production of vascular thrombi. What effect hypophysectomy, performed for its ameliorating effect upon bone metastases, will have upon these thrombotic manifestations will be a point of interest.

EFFECT OF ANTICOAGULANTS IN MULTIPLE THROMBOPHLEBITIS

Wright [6] has made the significant observation that anticoagulant therapy in thrombophlebitis associated with malignant disease may be effective in an early stage but that such therapy may be without long-range benefit; in other words, the thrombophlebitis may break through and recur despite the use of ordinary doses of anticoagulants. Wright has also properly emphasized that when there is a recurrence of the thrombosis during adequate therapy the likelihood of the presence of unproved carcinoma is much more to be suspected. This observation seems to be increasingly true if the patient is beyond the age limit of 35 or 40 years.

ETIOLOGICAL ASPECTS OF MULTIPLE THROMBOPHLEBITIS AND THROMBOPHLEBITIS MIGRANS

A comprehensive review of possible etiological factors pertaining to either of these conditions is not within the scope of this paper. The etiological mechanism should

‡ References 10 and 12.

provoke more than academic interest; potentially, it may very well be the means in the future of providing biochemical tests which will indicate the presence or absence of carcinoma.

A broad etiological concept presupposes the elaboration of a substance by the tumor cells which directly or indirectly influences the clotting mechanism to the extent that a characteristic type of thrombophlebitis occurs. Numerous attempts have failed to substantiate this hypothesis. For example, since the normal serum inhibitor against trypsin is frequently elevated in patients with carcinoma it was hoped that a measurement of this inhibitor might show a consistent increase sufficient to prove the presence of carcinoma; however, Peacock and Sheehy[18] failed to find any significantly increased value in the study of 648 patients with cancer.

Since thrombophlebitis migrans occurs predominantly in carcinoma of the pancreas, there is, of course, the intriguing speculation about the effects of mucolytic and other proteolytic enzymes upon the clotting mechanism. Evidence suggests that the vascular thromboses are probably not from immediate or direct action of, or lack of, amylase, protease, or lipase. Thus far, apparently no correlation of our knowledge of enzyme physiopathology permits any final deductions.

Many other possible factors have been proposed, directed more particularly to those cases of malignant disease not involving the pancreas. Differences in isoelectric potentials have been found in the area of the vein wall in ordinary thrombi, but I have observed no reports of such measurements in thrombophlebitis migrans. Changes in antithrombin titers, depression of A-C globulin, an alleged increase in prothrombin activators in carcinoma, platelet adhesiveness, mobilization of thrombocytosin, and numerous other investigations have been reported to show significant alterations, but no acceptable or proved etiological factor has yet been presented.

SUMMARY AND CONCLUSIONS

From this review of reported observations concerning the two types of carcinogenetic thrombophlebitis, the following statements may be made:

Of these two recognized types, one is indistinguishable from classical thrombophlebitis; the other presents the characteristic lesions of thrombophlebitis migrans.

The occurrence of either type, particularly in a male patient beyond the age of 35 years, warrants a presumptive diagnosis of visceral carcinoma until disproved.

Prompt recognition of either of these types of thrombophlebitis may permit detection of carcinoma months earlier than it might otherwise be discovered, thus affording more prompt use of protective anticoagulant therapy and perhaps more successful surgical procedures.

Unsuccessful control of thrombophlebitis by ordinary doses of anticoagulants should cause the clinician to suspect the presence of carcinoma.

The presence of typical lesions of thrombophlebitis migrans is usually pathognomonic of well-advanced visceral carcinoma.

A better understanding of the associated factors concerned in carcinogenetic thrombophlebitis should throw new light on the entire problem of thrombogenesis.

A more complete analysis of the biochemical changes involved in the etiology of these types of thrombophlebitis may also reveal or provide a reliable test for the presence of carcinoma, a goal for which the medical world is waiting.

ABSTRACT OF DISCUSSION

Dr. J. Earle Estes Jr., Rochester, Minn.: Thrombophlebitis should be considered not as a disease entity per se but as a signal that some basic pathologic state may exist elsewhere in the body of the person afflicted. Systemic diseases in which single or recurrent episodes of thrombophlebitis are known to occur include thromboangiitis obliterans; blood dyscrasias, such as polycythemia vera, leukemias, and anemias, and heart disease, such as myocardial infarction or cardiac decompensation. Any infectious disease may have as one of its manifestations an episode of thrombophlebitis. The occurrence of the latter in the postoperative and postpartum states is well known. Local disturbances such as trauma, intravenous infusions, or

localized infections may result in thrombophlebitis due to direct involvement of a vein.

As Dr. Durham has so ably emphasized, the association of thrombophlebitis and malignant tumors of viscera has been referred to by several medical authors. It has been demonstrated that carcinoma of the pancreas is the neoplasm most frequently complicated by episodes of thrombophlebitis. In addition, malignant tumors of the pelvis, retroperitoneal space, abdomen, thorax, and neck have been similarly implicated, although with lesser frequency. Specific organs, malignant tumors of which have been associated with episodes of thrombophlebitis in my experience, are listed in the Table. In my opinion, almost any extensive malignant process may have, as one of its manifestations, episodes of thrombophlebitis, involving either superficial or deep veins. It has been suggested that such episodes might assist physicians in making an "early" diagnosis of malignant tumors. However, the experience of my associates and me has been that when such episodes occur as manifestations of malignant disease they constitute almost without exception evidence of inoperability due to metastasis or extensive local invasion or both.

After all possible causes for thrombophlebitis have been considered, however, there remains a group of patients in whom thrombophlebitis develops without apparent cause. For lack of a better understanding of the abnormal physiology involved, these patients are said to have idiopathic thrombophlebitis. This may occur in single or multiple episodes; if multiple, the term "recurrent idiopathic thrombophlebitis" may be used. The term "thrombophlebitis migrans" has been used to designate this syndrome as well as other instances of recurrent thrombophlebitis regardless of what the underlying cause may have been. I believe that there is valid objection to use of the term "thrombophlebitis migrans" because of the connotation that this represents a distinct entity. My associates and I feel that it is not possible to identify different types of thrombophlebitis from the clinicopathologic standpoint. Thrombophlebitis occurring as a manifestation of malignant disease, infection, or heart disease, for example, is indistinguishable from that occurring in the postoperative or postpartum state, in leukemia, or idiopathically. Nor have we recognized a syndrome of thrombophlebitis associated with vegetations on the heart valves productive of arterial emboli.

Malignant Tumors and Thrombophlebitis: Organs Involved

Neck	Pelvis
Thyroid	Ovary
Larynx	Uterus
Thorax	Prostate
Breast	Rectum
Lung	Retroperitoneal space
Abdomen	Kidney
Stomach	Lymphosarcoma
Gall bladder	Liposarcoma
Liver	Miscellaneous
Pancreas	Osteogenic sarcoma
Colon	Lymphosarcoma, Hodgkin's disease
	Plasmacytoma

In what appears to be idiopathic thrombophlebitis it becomes important at times to distinguish between a single and a recurrent episode. Ackerman and Estes (Ackerman, R. F., and Estes, J. E.: Prognosis in Idiopathic Thrombophlebitis, *Ann. Int. Med.* **34**:902-910 [April] 1951) studied 88 patients who had had single or recurrent episodes of thrombophlebitis without apparent cause. These patients were followed for at least five years. Of 29 patients classified as having had a single episode of idiopathic thrombophlebitis, only 2 experienced a subsequent recurrence and only 1 experienced a subsequent disease that may have been related to the thrombophlebitis. The last-mentioned patient was a woman in whom cancer of the breast developed seven years after a single episode of thrombophlebitis. It seems doubtful that the two conditions are related in this instance. On the other hand, of 59 patients classified as having had recurrent episodes of idiopathic thrombophlebitis, 25 continued to have recurrences and 8 experienced some disease that may have been related to their thrombophlebitis; the possibly related disease was a malignant one in 5 of the 8 patients, polycythemia vera in 1, and thromboangiitis obliterans in 2.

Thus, it may be seen that it is important to distinguish between patients who have had a single episode and those who have had multiple episodes of idiopathic thrombophlebitis. When confronted with a patient who has had a recent single episode of thrombophlebitis and who has no evidence of a cause for this after thorough examination and routine laboratory investigation, I ordinarily do not press the investigation further. However, patients who have had two or more recent episodes of thrombophlebitis should have a searching investigation for causative disease, particularly for a malignant neoplasm.

In closing, I would like to reemphasize the diagnostic significance of thrombophlebitis that recurs in spite of anticoagulant therapy productive of therapeutic levels of plasma-prothrombin activity. This is almost always evidence of a malignant tumor that is inoperable.

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Anthrax

A Report of One Hundred Seventeen Cases

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Since 1933, I have had the opportunity to study 117 cases of anthrax, 116 of which were of the external or cutaneous type and 1, of the internal, or pulmonary, variety. In all cases, the clinical diagnosis was confirmed bacteriologically by means of suitable smears and cultures performed at the Chester Hospital by Dr. G. B. Sickel. As reported in a previous communication,[1] virulence tests done on guinea pigs, rabbits, and sheep with anthrax bacilli recovered from some of the cases revealed them to be highly virulent strains.

CUTANEOUS ANTHRAX

In this series, one patient, the very first case, died, giving a mortality rate of 0.8%. The subsequent 115 cases recovered without any sequelae. One hundred four originated in a local mill that uses goat hair in the manufacture of interlining for men's coats. The hair is imported from the Orient (China, India, Pakistan) and North Africa (Morocco) in accordance with existing but totally inadequate federal regulations. Six cases occurred in a subsidiary Philadelphia plant through the use of contaminated hair bobbins; one was in a driver who had hauled a truck-load of bales of hair a few months before he developed anthrax of the neck; four were in persons who lived in the village attached to the mill (three of these were children); one case was a girl of 12 who contracted anthrax after washing her father's work-shirt (carder).

Widespread dissemination of anthrax bacilli throughout the local plant is evidenced by the distribution of cases through the various departments (Table 1). Collateral studies performed in 1955 * resulted in the recovery of Bacillus anthracis from air samples and dust collected from machinery, walls, floors, clothing, and body surfaces of workers in practically every department of the mill.

TABLE 1.—*Distribution of Anthrax Cases*

	Cases, No.
Department of local mill	
Spinning	41
Drawing	12
Carding	33
Finishing	4
Doffing	3
Burling	4
Warehouse	5
Sweeper	1
Machinist	1
	104
Philadelphia Mill	6
Trucker	1
Village resident	1
Children	4
Grand total of cases	116

The monthly and yearly distribution of cases is shown in Table 2; the sharp increase noted in 1940 and 1941 is undoubtedly related to World War II and the resulting relaxation of regulations at the port of exit, as predicted by Smyth.[2] The cases occurred a few at a time, in close succession, and were

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* Anthrax sampling program carried out under supervision of Camp Detrick and U. S. Public Health Service personnel.

TABLE 2.—*Seasonal and Yearly Distribution of Anthrax Cases*

Month	Cases, No.	Year	Cases, No.
Jan.	7	1933	6
		1934	2
Feb.	16	1935	3
		1936	2
March	16	1937	4
		1938	2
April	7	1939	6
		1940	12
May	10	1941	15
		1942	8
June	9	1943	5
		1944	7
July	10	1945	3
		1947	1
Aug.	9	1948	4
		1949	4
Sept.	4	1950	10
		1951	6
Oct.	9	1952	5
		1953	3
Nov.	11	1954	6
		1955	2
Dec.	8		
	116		116

usually related to the passage through the mill of a new batch of hair. No monthly or seasonal increase, as such, was noted in this series; any variation is most likely related to the seasonal demands of the clothing trade.

Fifty-nine patients were male, and fifty-seven were female; all but five were white. Their ages ranged from 3½ to 62 years. The sex and color incidence simply reflect the number of white females employed in this particular industry.

The location of the lesion is shown in Table 3; 47 patients had anthrax of the face and neck, sites associated in the past with the highest mortality rate.[2]

Definite trauma to the skin was present in many of the cases; usually it consisted of a minor scratch. On several occasions I noted that some workers with severe multiple puncture wounds contracted on heavily contaminated carding machines escaped anthrax, while subsequently, after a minor scratch, they developed a typical lesion. Whether this was due to the vagaries of chance or to variations in individual resistance is not known. In some patients, no history or evidence of local injury was found.

TABLE 3.—*Site of Anthrax Lesion*

Location	Cases, No.
Face	34
Neck	13
Arm	7
Forearm	28
Hand	8
Finger	22
Leg	3
Heel	1
Total	116

The incubation period in this series varied from 12 hours to 5 days, with an average of 3 days.

The appearance of the lesion differs with its age. Very early, it looks like a flea-bite

Fig. 1 (Case 115).—Note the large tense single vesicle with surrounding edema. It is occasionally seen early in anthrax (first two days). The center of the vesicle ulcerated and became the seat of eschar formation.

or tiny pimple. In a few hours, the papule enlarges and appears fleshy. Soon its top turns brown and is surrounded by a ring of erythema. On the second day, fine tight shiny yellow vesicles encircle the apex of the papule, and painless nonpitting edema appears and soon spreads beyond the papule's vicinity. I have seen this edema reach the level of the iliac crest in anthrax of the neck. Occasionally, a single large tense vesicle is seen enclosing the papule (Fig. 1). As the vesicles enlarge, they discharge a serosanguineous fluid rich in anthrax bacilli but

Fig. 2 (Case 117).—Lesion consists of a large hemorrhagic vesicle surrounding the original site of trauma that looked like a "torn hang nail." Edema of the midfinger present.

poor in cellular content, and the depressed center of the papule turns brown until the third or fourth day, when it becomes black. On the fifth to seventh day, a tough dry eschar covers the center of the ulcer and soon spreads into the crusting peripheral vesicles. Thereafter, the eschar separates at the periphery, and at the end of 12 to 14 days it sloughs out, leaving a shallow ulcer that heals by granulation (Figs. 2-5). In toxic cases, the edema is accompanied by lymphangitis and/or cellulitis of the overlying skin, with considerable local pain and tenderness, but as soon as this inflammatory reaction subsides the anthrax lesion becomes painless again. Itching at the site of the papule may be an early and striking complaint. Regional adenopathy is usually present in the first few days; its clinical detection may be preceded by considerable local pain and tenderness, in contrast to the anthrax lesion and edema, which are characteristically painless. The adenopathy may be accompanied by edema of the overlying soft tissues and may remain palpable but otherwise asymptomatic for days or weeks after the lesion has healed.

Signs of systemic reaction varied in these patients. Some were asymptomatic, but most of them had headache, malaise, and fever ranging from 99.2 to 102 F or higher; blood cell counts were most frequently within normal limits; in a few patients a neutrophilic leucocytosis (from 10,500 to 13,500) was seen. Blood cultures were sterile in all patients. Even in Case 1, the blood culture made 39 hours before death was negative for B. anthracis, but at autopsy the organism was recovered from various organs.

TREATMENT

The first 21 cases were treated with anti-anthrax serum. Each patient required an optimum dose that varied from 250 to over 1000 cc. of serum given intravenously.† This

† References 3 and 4.

Fig. 3 (Case 26).—Typical lesion, three to four days old. The center is dry, black, and surrounded by a ring of vesicles that contain a hemorrhagic fluid. Painless edema encircles the anthrax lesion.

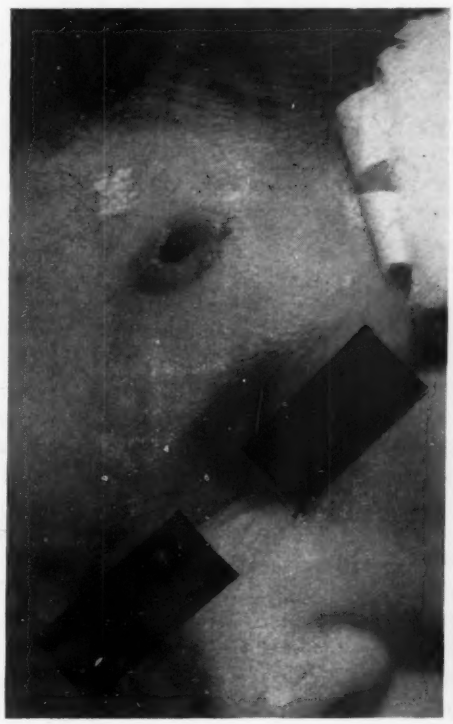

Fig. 4 (Case 8).—Note the extensive edema that surrounds the anthrax lesion.

therapy, although effective, resulted in prolonged morbidity, from the severe horse-serum sensitivity reactions that ensued. In 1939 I tried the sulfonamides and found them to be efficacious in the treatment of anthrax. Sulfathiazole was considered the drug of choice.[1] An initial dose of 2 to 3 gm. followed by 1 gm. every four hours for 2 to 3 days served to check the spread of the edema, with subsidence of fever, tachycardia, and malaise. Thereafter, the drug was continued at a lower dose until the local signs of anthrax infection subsided and the organism was no longer recovered on culture from the lesion. When an occasional failure was encountered I resorted to antianthrax serum. By 1947, I had successfully treated 56 cases with the various sulfonamides, most of them as ambulatory patients, with marked decrease in the morbidity and cost of illness. As expected, reactions to the sulfa drugs such as vertigo, hematuria, urticaria, and dermatitis were encountered rather frequently, but the advantages of this form of chemotherapy were so great that the serum was seldom used. The last member of this group (Case 76), with a lesion of the forearm, proved refractory to high doses of sulfathiazole, but the spreading edema and lymphangitis were brought under control within 24 hours after the injection of 100,000 units of crystalline penicillin followed by 40,000 units every 3 hours. Thereafter, I used penicillin and the broad-spectrum antibiotics exclusively in the treatment of anthrax.

In vitro sensitization tests performed with anthrax bacilli recovered from some of these patients demonstrated marked sensitivity of the organism to oxytetracycline (Terramycin), erythromycin, chlortetracycline (Aureomycin), chloramphenicol (Chloromycetin), tetracycline (Achromycin), penicillin, and streptomycin and resistance to neomycin and polymyxin (Tables 4 and 5).

Five patients were treated with penicillin, either crystalline or in repository form. I prefer to give a large initial dose of crystalline penicillin (100,000 to 500,000 units), followed by either 20,000 to 50,000 units every 3 to 4 hours or 600,000 units of penicillin procaine suspension every 12 to 24 hours, depending on the location and severity of the infection. In 24 to 48 hours, the spread of the edema is checked and the local erythema, if present, subsides. Thereafter, the dosage of penicillin is reduced to 300,000 to 600,000 units daily, but treatment is continued until the edema clears completely (two to three days). Painless adenopathy may persist for days or weeks and is no indication for continued therapy. The papule

Fig. 5 (Case 23).—Large eschar separating at the periphery of the anthrax lesion. Ring of vesicles, dry and crusty. Edema has subsided.

TABLE 4.—*Bacterial Sensitivity Tests* *

Case No.	Aureomycin, γ	Chloramphenicol, γ	Penicillin, γ	Streptomycin, γ	Neomycin, γ	Polymyxin, γ	Oxytetracycline, γ
84	pi 0.1† ci 1.0	3.12	<0.1	3.12	5.0	>25.0	<0.1
85	pi 0.1 ci 1.0	3.12	pi 0.1 ci 1.0	pi 3.12 ci 12.50	5.0	>25.0	<0.1
86	pi 0.1 ci 1.0	3.12	<0.1	pi 3.12 ci 12.50	5.0	>25.0	<0.1
87	pi 0.1 ci 1.0	3.12	pi 0.1 ci 1.0	pi 3.12 ci 12.50	5.0	>25.0	<0.1
88	<0.1	12.50	pi 1.0 ci 5.0	pi 3.12 ci 12.50	pi 5.0 ci 25.0	>25.0	<0.1
89	<0.1	pi 3.12 ci 12.50	pi 1.0 ci 5.0	pi 3.12 ci 12.50	pi 5.0 ci 25.0	>25.0	<0.1
90	<0.1	pi 3.12 ci 12.50	<0.1	pi 3.12 ci 12.50	5.0	>25.0	<0.1
91	<0.1	pi 3.12 ci 12.50	pi 0.1 ci 1.0	3.12	5.0	>25.0	<0.1
92	<0.1	3.12	1.0	3.12	5.0	>25.0	<0.1
93	<0.1	pi 3.12 ci 12.50	<0.1	pi 3.12 ci 12.50			<0.1
94	<0.1	pi 3.12 ci 12.50	<0.1	pi 3.12 ci 12.50			<0.1

* Performed in the Laboratory of the Division of Infectious Diseases of the Hospital of the University of Pennsylvania through the courtesy of Dr. W. P. Boger. (From Practice of Medicine, edited by F. Tice, Hagerstown, Md., F. W. Prior Company, Inc., Vol. 5, p. 17.)

† Pi, partial inhibition; ci, complete inhibition.

TABLE 5.—*Bacterial Sensitivity Tests* *

Case No.	Chlortetracycline, 4 γ/Ml.	Chloramphenicol, 15 γ/Ml.	Penicillin, 1 Unit/Ml.	Streptomycin, 15 γ/Ml.	Oxytetracycline, 6 γ/Ml.	Tetracycline, 5 γ/Ml.	Serial Dilutions: Sensitive to Erythromycin	Serial Dilutions: Sensitive to Tetracycline
110	Sensitive	Sensitive	Sensitive	Sensitive	Sensitive	.....	0.19 γ/ml.	0.048 γ/ml.
111	Sensitive	Sensitive	Sensitive	Sensitive	Sensitive	.....	0.09 γ/ml.	12.4 γ/ml.
113	Sensitive	Sensitive	Sensitive	Sensitive	Sensitive	Sensitive	.....	.....
115	Sensitive	Sensitive	Sensitive	Sensitive	Sensitive	Sensitive	0.195 γ/ml.	.....

* Performed in the Laboratory of the Division of Infectious Diseases of the Hospital of the University of Pennsylvania through the courtesy of Dr. E. L. Foltz.

TABLE 6.—*Plasma Levels of Antibiotics*

Case	Drug	Dose, Mg.	Plasma Levels, γ/Ml. After Oral Dose*: ½ Hour	1 Hour	2 Hours	3 Hours	4 Hours	6 Hours
86	Oxytetracycline	500	8	16	16	..	16	..
87	Oxytetracycline	750	8	16	16	..	16	..
90	Oxytetracycline	500	8	16	16	..	16	..
91	Oxytetracycline	500	8	16	16	..	16	..
92	Oxytetracycline	500	..	16	..	..	16	..
	Chloramphenicol	750	..	120	120	90	60	..
84	Chloramphenicol	250	..	..	<7.5	..	<7.5	<7.5
85	Chloramphenicol	1,000	..	..	60	..	45	30
	Chloramphenicol	500	..	..	20	..	10	5
88	Chloramphenicol	500	..	20	20	10	20	..
89	Chloramphenicol	750	..	20	15	7.5	15.0	..
93	Chloramphenicol	750	..	22.6	30	22.6	..	..
94	Chloramphenicol	750	..	22.6	30	15	15	..

* Performed in the Laboratory of the Division of Infectious Diseases of the Hospital of the University of Pennsylvania through the courtesy of Dr. W. P. Boger. (From Practice of Medicine, edited by F. Tice, Hagerstown, Md., F. W. Prior Company, Inc., Vol. 5, p. 19.)

itself does not seem to be affected by the treatment given; it goes through its various stages as described. However, in most cases anthrax bacilli disappeared from the lesion in 24 to 48 hours. In one case (Case 101) B. anthracis was recovered from the lesion 60 hours after treatment was begun and the patient had received a total of 3,300,000 units of penicillin in oil. In this group of patients, the total dose of penicillin ranged from 980,000 to 6,000,000 units, given in from two to seven days, respectively.

In general, penicillin was found to be a very effective agent in the treatment of anthrax. However, some patients object to multiple injections, sensitization reactions do occur, and hospitalization may be necessary, thus increasing the cost of medical care.

Six cases were treated with chlortetracycline given by mouth. After a somewhat larger initial dose, 500 to 750 mg. was administered every four to six hours for the first day or two, or until the spread of the edema was checked; thereafter, the dose was reduced to 250 to 500 mg. and/or the interval between doses was prolonged. As was noted with penicillin, a temporary increase in the edema during the first 24 hours of treatment with chlortetracycline and the other broad-spectrum antibiotics was recorded in some patients. The total dose of chlortetracycline varied from 4.5 gm. in 24 hours to 20.5 gm. in 8 days. The large doses used resulted in troublesome nausea and vomiting in some patients.

Seven cases were treated with chloramphenicol. After an initial dose of 1 gm., 0.75 gm. was given every 4 hours until the edema subsided, usually in 24 to 48 hours; thereafter the dose was gradually reduced. The total dose ranged from 2.5 gm. in two days to 24.75 gm. in seven days. Chloramphenicol was found to be an excellent therapeutic agent for anthrax, but its use was discontinued after the reports of its depressive effect on hemopoiesis.

Fifteen patients were treated with oxytetracycline, with excellent results in fourteen. The failure (Case 92, anthrax of forearm) did not respond after 36 hours of intensive therapy with this antibiotic and was then cured by chloramphenicol. The average initial dose of oxytetracycline was 1 gm., followed by 0.75 gm. every four hours until the local signs of spreading disease were under control. This usually took 24 to 48 hours. The total dose given ranged from 3.0 gm. in three days to 29.5 gm. in eight days. The drug was well tolerated by all patients.

Six patients were treated with tetracycline, with excellent results. The average individual dose was 500 mg. every four to six hours; the total dose ranged from 10 gm. in five and one-half days to 14 gm. in eight days.

Two patients were successfully treated with erythromycin: 200 mg. was given every four hours for two to three days; thereafter the dose was reduced to 100 mg. every four to six hours. The total dose ranged from 3.2 gm. in 90 hours to 5.6 gm. in 7 days. The drug was well tolerated.

Positive cultures from the lesion were obtained in the patients treated with the broad-spectrum antibiotics for a period of two to five days, a somewhat longer interval than in the penicillin-treated group.

It is clear that anthrax must be treated systemically and that the modern antibiotics provide us with suitable therapeutic agents. The treatment given in this series was highly individualized, and the dose used was arbitrary; perhaps a much smaller amount of antibiotic would have sufficed. However, I felt it advisable to err on the side of conservatism; the aim was to secure a blood level of a given antibiotic several times its effective in vitro concentration. Titrations were carried out in some patients, and the values obtained are shown in Table 6. The affected part should be placed at rest; the lesion should be suitably covered with a sterile dressing, which no one but the medical attendant must be allowed to remove and properly dispose of. Locally, I have used chlortetracycline and oxytetracycline ointment, and streptokinase to digest the eschar, without significant results. The local applica-

tion of tincture of iodine and/or phenol is contraindicated, since it does not prevent anthrax and may otherwise be harmful.

PULMONARY ANTHRAX

I have seen only one case of pulmonary anthrax; because of its rarity a summary of the clinical and autopsy findings is given.

A white man, 42 years of age, had worked for several months in the local mill as a handyman in the carding room. One of his chief tasks was the cleaning of the cards and disposal of the dust. He had been in good health and working until May 30, 1942, when he became nauseated and developed a severe chill and fever of 103 F and pains throughout the chest, back, and upper abdomen. He became very short of breath and vomited several times. The patient was seen at home by his family physician, who made a diagnosis of brochopneumonia and treated him with sulfathiazole, 1.0 gm. every four hours, without any improvement. When this man's illness was reported to his employers, I was asked to see the patient, on June 2, 1942. At this time he appeared to be extremely apprehensive and coughed in paroxysms, without being able to bring up any sputum; there was marked cyanosis with grayish appearance of the skin, which was warm and wet; dehydration was marked; temperature was 101 F; pulse was regular and rapid; the signs in the chest revealed a left lower pneumonia. The patient was admitted to the Chester Hospital on the same day. The temperature was 100 F; the pulse rate 100; respirations, 32 per minute, and the blood pressure 110/50. On June 3, urinalysis was within normal limits; hemoglobin was 17.0 gm.; RBC count was 5,420,000; WBC, 19,000, with 89% polymorphonuclear cells and 11% lymphocytes. X-ray of the chest revealed the following: "consolidation in the left basal lobe; a small amount of effusion displaced the heart slightly to the right and flattened the right leaf of the diaphragm. Moderate hilar thickening and accentuation of linear striations were evident." The patient was treated with fluids intravenously to overcome the dehydration and sulfadiazine, 1.0 gm. every three hours. No sputum could be obtained; however, on June 3, 1942, a nasopharyngeal smear and culture were secured, but the bacteriological report of anthrax did not become available until just after the patient's death. During his short period of hospitalization, the patient became quite agitated and restless; dyspnea and cyanosis became very pronounced, and the lungs filled with coarse large and small rales. The temperature rose to 101 F, the pulse rate was 140, and the respirations were 40 per minute. Notwithstanding supportive measures, he died suddenly, on June 4, 1942, at 1:34 a. m.

An autopsy was performed on the same day, by Dr. G. B. Sickel; it showed the following pertinent data: Gross findings: Both pleural cavities contained a large amount of slightly cloudy, straw-colored fluid. The lungs weighed 1390 gm., and their external surface was purplish-red, very smooth and glistening. Both lower lobes were very edematous, more so on the left, and a cloudy fluid oozed from the cut surface. The upper lobes were little affected. The spleen was not enlarged but was much softer than normal. On section, it was dark red and the Malpighian bodies were prominent. A culture taken from the heart's blood at necropsy showed anthrax bacilli. Microscopic examination revealed passive congestion of the liver and spleen; the kidneys displayed evidences of acute glomerulitis; sections of the lung showed numerous areas of hemorrhage within the alveolar spaces, some of which contained fibrinous material. There was a moderate lymphocytic infiltration in the alveolar walls, with special prominence around some of the vessels and bronchioles. Within the alveolar spaces there were a large number of macrophages containing black pigment granules. Occasionally polymorphonuclear leucocytes were noted scattered about. The bronchioles contained mucoid material and a few red cells and lymphocytes. The picture seen was interpreted as due to an interstitial type of pneumonitis.

It is unfortunate that the etiologic agent of this patient's pneumonia was not determined sooner and that more vigorous treatment was not instituted earlier. With the present availability of penicillin and the broad-spectrum antibiotics, one should expect successful results in the treatment of anthrax pneumonia provided the correct diagnosis is made early enough.

I have not seen any cases of anthrax infection of the gastrointestinal tract or of the central nervous system, but successful results in the treatment of anthrax meningitis have been reported.[10]

COMMENT

Although some patients recover from anthrax without any treatment, as exemplified by one of our cases (Case 68, with a lesion on the arm), it is clear that the prompt recognition of anthrax is essential for its successful management. Penicillin and the broad-spectrum antibiotics are excellent therapeutic agents when employed in adequate doses. The latter have simplified the management of anthrax so that one can

Fig. 6 (Case 100).—Very extensive eschar covering burnt extensor surface of forearm and hand.

safely say that, in man, this disease has lost its past serious connotations. The death percentage rate in the U. S. A. was 23+ from 1919 to 1923; 20+ from 1924 to 1928; 22+ from 1929 to 1933, and 16+ from 1933 to 1938.[2] Since the advent of penicillin, large series of anthrax cases have been reported by various workers ‡ without a single death. It is not known whether antibiotics prevent the disease if given soon after injury, during the incubation period. I had a patient with a laceration of the thumb from which anthrax bacilli were recovered; yet upon treatment with oxytetracycline (0.5 gm. every four hours) he failed to develop any clinically recognizable anthrax lesion. On the other hand, another patient (Case 100), who was severely injured with multiple compound fractures and deep third degree burns of the right forearm, was given large doses of penicillin daily immediately following the injury; yet on the fifth day he developed the most extensive anthrax lesion I have seen. The eschar covered the entire extensor surface of the forearm from the metacarpophalangeal joints to just below the elbow (Fig. 6). He recovered after further treatment with penicillin, oxytetracycline, and chloramphenicol.

‡ References 5-9.

I cannot account for the scarcity of cases of pulmonary infection in the presence of virulent anthrax bacilli in the dust and air which is being inhaled by the workers of this particular plant. This is in marked contrast to the past experience in England, where woolsorter's disease, or pulmonary anthrax, was a very common occurrence in the textile industry. The role played by particle size of the inhaled dust is now under study. I am also unable to explain the very small yearly number of cases of anthrax of the skin encountered by us in the presence of such widespread dissemination of anthrax bacilli in the plant. I do not believe that this is related to the incidence of injury to the skin, because the latter is very prevalent in this industry, and in some cases trauma either was completely absent or was so trivial as to escape the attention of the person who contracted anthrax. Moreover, in a patient with a laceration of the hand anthrax bacilli were recovered on smear and culture of the wound yet no clinical infection with the production of an anthrax papule ever developed. It is probable that individual immunity may account for the variation in the incidence of clinical anthrax in these employees. If it exists, this immunity is apparently not related to the length of employment or exposure, because I have seen anthrax develop in workers after many years of unchanged occupation as well as in newly engaged laborers after only a few weeks of employment. As yet, I have not seen a repeat or second infection upon return to work in patients who had recovered from anthrax. However, Hodgson has reported such cases.[11]

Experimentally, only protection tests can be used to measure immunity, and this method has been employed by Wright and his associates [12] to determine in animals the value of an alum-precipitated protective antigen which they have prepared by growing a nonproteolytic mutant strain of anthrax bacillus in a chemically-defined nonprotein medium. At present, we are engaged in a field study to determine the value of this antigen in the prevention of anthrax among

workers exposed to this disease. Our findings will be the subject of a separate report.

SUMMARY AND CONCLUSIONS

The experience with 117 cases of anthrax is reviewed. One hundred sixteen had cutaneous anthrax; one patient had pulmonary anthrax.

The source of infection was contaminated imported goat hair used in the manufacture of interlining of suits.

In the series of cutaneous anthrax, the first patient died, giving a mortality rate of 0.8%. The patient with pulmonary infection died. Autopsy findings are given.

Early, prompt recognition of anthrax is essential. Treatment with penicillin or broad-spectrum antibiotics offers the best chance of cure, provided adequate dosage is used. Control of the spreading edema, with subsidence of systemic toxicity, is the only reliable yardstick with which to measure adequate dosage.

The broad-spectrum antibiotics are easy to administer, cause few or no reactions, and make ambulatory treatment of these patients possible.

Chlortetracycline (Aureomycin), oxytetracycline (Terramycin), tetracycline (Achromycin), and erythromycin work equally well and are the drugs of choice in the treatment of anthrax.

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ABSTRACT OF DISCUSSION

E. L. Foltz, M.D., Philadelphia: There can be little room for doubt that antibiotics and chemotherapy have provided the physician with effective weapons in the battle against clinical anthrax. Dr. Gold's report certainly summarizes a wide experience with a variety of curative agents, and it appears that practically all commonly used antibiotics are effective in the control of cutaneous anthrax; this adds clinical confirmation to the laboratory studies which have shown susceptibility to a wide variety of antimicrobial substances. Relatively few cases of pulmonary anthrax treated with antibiotics are available to compare the efficacy of treatment with different agents. There are also cases of anthrax meningitis which have failed to respond to antibiotics either because they have received treatment too late or have been inadequately treated.

It is obvious, then, that the first requisite for successful treatment of anthrax is prompt recognition of the disease; in the absence of the cutaneous lesion, the diagnosis rests primarily with the laboratory. However, this does not mean that the therapeutic program should be delayed in a suspected case. The drug of choice still appears to be penicillin. Although Dr. Gold's results with the broad-spectrum antibiotics have been excellent, the fact that clinical responses in general are slower to these agents, and also that Dr. Gold isolated positive cultures of anthrax for longer periods of time from treated cutaneous lesions after broad-spectrum drugs, diminishes personal enthusiasm for these agents in this disease. The dosage will vary with the type of infection, and I would certainly recommend use of heavier doses than those preferred by Dr. Gold when dealing with the pulmonary or meningitic form of the disease.

The prevention of the disease seems of equal importance. Approximately 75% of all cases in the United States occur in the northeastern states, chiefly as the result of industrial exposure. Tanneries and processing plants for animal hairs and wool are the chief industrial sources of infection. Methods of sterilization which would be effective in eradicating the anthrax spores from contaminated hides and animal hairs are unacceptable to the industries; heating or chemical sterilization procedures so alter the physical properties of hides and animal hair as to render them valueless for commercial use. Sterilization of other contaminated animal products, such as bonemeal, is readily accomplished and is a part of federal as well as some state public-health control programs. The problem in agricultural areas is even greater but fortunately results in fewer clinical cases.

Prevention therefore becomes a problem of immunity. Apparently subsequent infections after initially proved anthrax are rare; this suggests some immune mechanism. Vaccination trials in the past met with no great success because of lack of an adequate vaccine. Recent work by Wright and others at Camp Detrick, Md., with an alum-precipitated protective antigen has demonstrated animal immunity for short periods against sizeable challenge doses in experimental infections. The antigen has been used in volunteers with no systemic reactions and only an occasional local reaction; no report on the effectiveness in man is available, since no serological test has been developed to measure the immune response. On the other hand, the demonstration of antibodies is no guarantee of immunity, and perhaps the best demonstration of effectiveness is in a controlled study of those exposed to the disease. Perhaps Dr. Gold would care to comment on these studies and tell us of any personal experience with immunization.

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Effects of Adrenal Steroids on Resistance to Infection

Differences in the Relative Amounts of Corticosterone and Hydrocortisone Secreted and in Their Biologic Effects

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The predominant adrenal steroids of all animal species that have been studied are hydrocortisone (17-hydroxycorticosterone, Cortisol, Kendall's Compound F) and corticosterone (Kendall's Compound B). The close association of these two steroids in different animal species has been studied extensively by Bush,[1] who found that the ratios of hydrocortisone to corticosterone in the adrenal vein blood were different for different animal species (Table 1). The data with respect to man are as yet incomplete, but the evidence suggests that the human adrenal cortex secretes hydrocortisone predominantly.

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From the Thorndike Memorial Laboratory, Second and Fourth Medical Services (Harvard), Boston City Hospital, Department of Medicine, Harvard Medical School (Drs. Kass and Mou); the Worcester Foundation for Experimental Biology (Dr. Hechter), and the Henry Phipps Institute, University of Pennsylvania (Dr. Lurie). Present address of Dr. Mou: Strong Memorial Hospital.

Despite many similar metabolic effects of hydrocortisone and corticosterone, and the efficacy of either drug in the treatment of adrenocortical insufficiency,[2] hydrocortisone is active in the treatment of clinical inflammatory disorders but corticosterone is inactive at the same dosage levels in the treatment of rheumatoid arthritis.[3]

The comparative effects of corticosterone and hydrocortisone on some aspects of resistance to infection were studied in the hope that the differences in the mode of action of these two substances would permit a separation of the anti-inflammatory effects of hydrocortisone from those general metabolic effects that are shared by corticosterone.

TABLE 1.—*Hydrocortisone to Corticosterone* (F/B) *Ratios in Adrenal Vein Blood of Various Animal Species**

	F/B Ratio
Monkey	>20
Dog	6
Cat	4-6
Sheep	15-20
Ox	1
Ferret	1-5
Rabbit	<0.05
Rat	<0.05

* Adapted from Bush,[1] *The Journal of Endocrinology*, London and New York, Cambridge University Press.

It was previously shown that hydrocortisone, like cortisone, increased the susceptibility of experimental animals to induced viral and bacterial infections whereas corticosterone was variable in its action and generally did not alter susceptibility to infection in the same dosage.*

These differences in the action of corticosterone and hydrocortisone on resistance

* References 4 and 5.

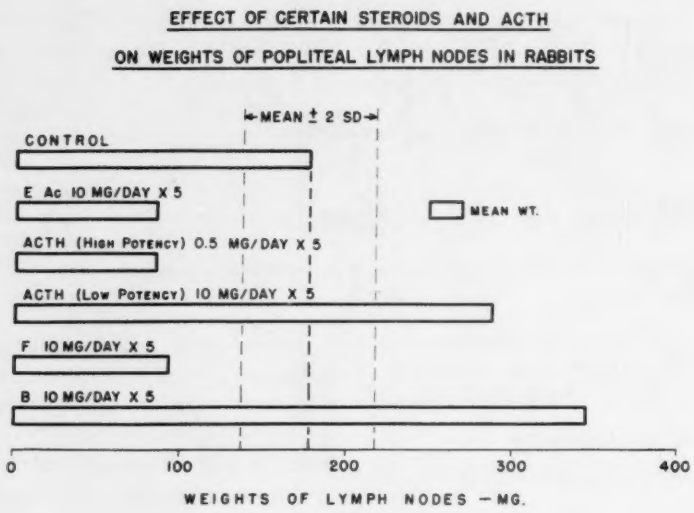

Figure 1.

to infection are probably quantitative rather than qualitative † and have not been studied in many animal species. Additional indications that corticosterone and hydrocortisone in the same dosages act differently in experimental infections in hamsters have appeared recently.[6]

In other experiments, hydrocortisone, given daily for five days to rabbits, produced atrophy of lymph nodes. The same amount of corticosterone induced mild transient hyperplasia (Fig. 1). Surprisingly, a low-potency preparation of corticotropin acted more like corticosterone, whereas a high-potency preparation acted more like hydrocortisone.

The atrophy that occurs in the lymph nodes is accompanied by extensive lysis of lymphocytes and disintegration of nuclei. When the nucleic acid changes within the lymph nodes of animals that had received hydrocortisone or cortisone were measured, it was found that the concentrations of deox-

† Frenkel, J. K.: Personal communication to the authors.

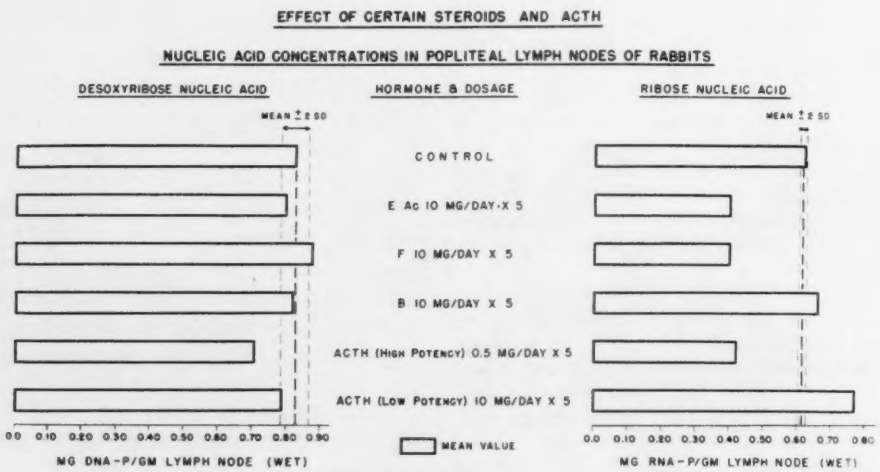
EFFECT OF CERTAIN STEROIDS AND ACTH
NUCLEIC ACID CONCENTRATIONS IN POPLITEAL LYMPH NODES OF RABBITS
DESOXYRIBOSE NUCLEIC ACID
HORMONE & DOSAGE
RIBOSE NUCLEIC ACID
MEAN ± 2 SD
CONTROL
E Ac 10 MG/DAY X 5
F 10 MG/DAY X 5
B 10 MG/DAY X 5
ACTH (High Potency) 0.5 MG/DAY X 5
ACTH (Low Potency) 10 MG/DAY X 5
MEAN VALUE
0.0 0.10 0.20 0.30 0.40 0.50 0.60 0.70 0.80 0.90
MG DNA-P/GM LYMPH NODE (WET)
MG RNA-P/GM LYMPH NODE (WET)

Figure 2.

yribonucleic acid changed very little, but those of ribonucleic acid decreased significantly (Fig. 2). Corticosterone had no significant effect, and corticotropin, once again, acted differently, depending upon the potency of the preparation, the impure, low-potency preparation acting more like corticosterone and the highly purified, high-potency preparation acting more like hydrocortisone.[7]

A troublesome contradiction in the data became increasingly apparent. Rabbits had been reported to produce corticosterone as the predominant adrenal steroid, yet the administration of corticotropin at times led to effects that were more like those of hydrocortisone.

Further study of the different effects of corticosterone and hydrocortisone on mechanisms of resistance to infection was indicated.

The effects of these adrenal steroids and of corticotropin on antibody production in rabbits were studied. Human serum gammaglobulin was given intramusclarly in 50 mg. doses suspended with aluminum hydroxide to groups of 3 to 10 animals. The animals were given the antigen three times weekly for two weeks; this dosage was followed by a rest period of 10 days and the first bleeding. A second course of three injections in one week was followed by a five-day rest period and the second bleeding. Hormone was administered during the entire 36-day period of immunization. Only the results of the second bleedings are given in Table 2, since they were obtained at the time of maximal antibody response. In addition, Table 2 indicates the maximal change in weight that occurred for the animals during the 36-day period of hormone administration. It is apparent that the same doses of corticosterone and hydrocortisone exerted strikingly different effects on the weights of the animals, and that even 2.5 mg. of hydrocortisone caused more weight loss than did 10 mg. of corticosterone. The corticotropin was a crude preparation and was suspended in peanut oil containing 5% beeswax.

Corticosterone in rather large doses exerted no significant effect on antibody production, as measured immunochemically. Hydrocortisone, in the same dosages, suppressed antibody production almost completely. One-fourth as much hydrocortisone permitted less than one-fifth of the control antibody titer.

A distant relationship between dosage of corticotropin and antibody titer was demonstrable; the larger amounts of corticotropin suppressed antibody production almost as much as did 2.5 mg. of hydrocortisone. Corticosterone did not antagonize the effects of hydrocortisone when both were given together but, instead, was mildly additive, with respect to effect both on weight and on antibody production. Corticosterone also did not overcome the adverse effects of hydrocortisone on experimental infections in mice.

TABLE 2.—*Effects of Hydrocortisone, Corticosterone, and Corticotropin on Antibody Production in Rabbits*

Hormonal Treatment	Change in Weight, %	Mean Maximal Concentration of Antibody, Mg./Ml.
None	+14	0.867
Corticosterone (10 mg./day)	+ 8	0.928
Hydrocortisone (10 mg./day)	−18	0.066
Hydrocortisone (2.5 mg./day)	− 1	0.144
Corticosterone (10 mg./day) + hydrocortisone (10 mg./day)	−20	0.029
Corticosterone (10 mg./day) + hydrocortisone (2.5 mg./day)	−13	0.015
Corticotropin (15 u./day)	+ 6	0.734
Corticotropin (20 u./day)	− 4	0.561
Corticotropin (30 u./day)	−11	0.348

The differences in the effects of different doses of corticotropin could not be explained readily on the basis that corticosterone was the predominant adrenal secretory product even after prolonged stimulation with corticotropin. Investigation of the adrenal secretion of rabbits was therefore undertaken.

A procedure for collecting adrenal vein blood was devised and, in confirmation of Bush's findings, corticosterone was the predominant steroid produced in the genetically heterogeneous laboratory strain of rabbits

TABLE 3.—*Effect of Administration of Corticotropin on Concentrations of Corticosterone and Hydrocortisone in Adrenal Vein Blood of 4 Groups of Rabbits*

Rabbits, No.	Corticotropin Treatment	Vol. of Sample (Ml.)	F,* γ/100 Ml.	B,* γ/100 Ml.	Ratio F/B
6	0 (control)	69	<6-8	155	<.05
5	Single dose	65	<6-8	140	<.05
4	7 days	50	62	126	0.5
5	21-28 days	60	307	75	4.0

* F, hydrocortisone; B, corticosterone.

(Table 3). Hydrocortisone was undetectable or present in trace amounts. A single intravenous injection of corticotropin, begun two hours before the operation and continued throughout the procedure, failed to alter the nature or amount of adrenal secretion, presumably because the operation alone stimulated adrenal release of steroid to its maximum.

When corticotropin was given daily for one week, however, substantial amounts of hydrocortisone appeared, and the ratio of hydrocortisone to corticosterone rose to 0.5. After three to four weeks of administration of corticosterone, there was four times as much hydrocortisone as corticosterone being produced.[8]

Endogenous stimuli of sufficient magnitude also induced alterations in the nature of the secretory product of the adrenal cortex. A few illustrative experiments are presented in Figure 3. In one study, the right ureter of each of five rabbits was ligated and the animals were injected intravenously with 1 ml. of an overnight culture of Escherichia coli. One week later blood was collected from the adrenal veins of these animals. Three of the rabbits were found to have developed an infected hydronephrosis, and two showed no bacteriologic evidence of infection. Four of the five rabbits increased their secretion of hydrocortisone substantially, but the total amount of secretion was variable and unpredictable. There was no correlation between the amount of steroid found in the adrenal effluent and either degree of spread of infection or changes in weight of the animals. In another experiment, four rabbits were given sterile abscesses by the intramuscular injection of 2 ml. of turpentine every two days. One week after the first injection, adrenal vein blood was collected and pooled for a single analysis. There was a substantial increase in hydrocortisone and a very large total steroid output.

These observations may explain why corticotropin acts differently under different circumstances. They also show that the nature of the adrenal secretory product in rabbits may vary, depending upon the circumstances. Certain stimuli may lead to alterations in the type as well as in the amount of adrenal steroid secreted.

The mechanism by which adrenal secretions may vary is not clear. Present evidence suggests that steroidogenesis follows the path shown in Figure 4 and that corticotropin acts only on the conversion of cholesterol to pregnenolone.[9] Manifestly such a scheme must be modified to account for the effects of corticotropin in increasing the activity of the 17-hydroxylating system within the adrenal cortex. The possibility also remains that different preparations of corticotropin may have different effects on steroidogenesis —the corticotropin used in these experiments was all of porcine origin—although the find-

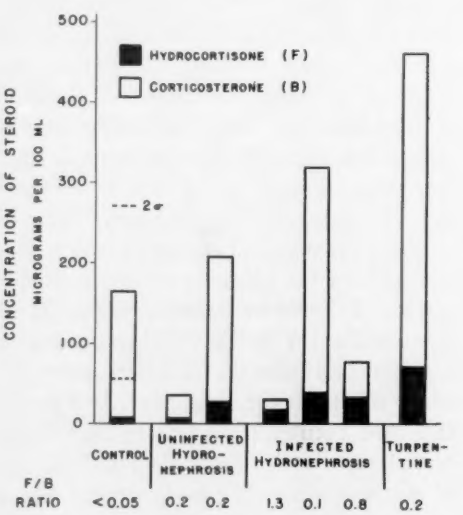

Fig. 3.—Concentration of steroid in adrenal vein blood following certain stimuli.

ing that endogenous stimuli such as sterile abscesses or infections may increase adrenal secretion of hydrocortisone makes the latter possibility unlikely.

Since there are such important differences between hydrocortisone and corticosterone with respect to their effect on mechanisms of resistance to infection, alterations in the nature of the adrenal secretion may be expected to alter host resistance in response to external stimuli, corticotropin, etc.

Indications of a relationship between alterations in adrenal secretion and resistance to tuberculosis have been obtained from the study of inbred strains of rabbits with genetically defined resistance to tuberculosis. When such animals are exposed to aerosols containing known numbers of human tubercle bacilli, the susceptible animals form one tubercle for each 20 to 80 inhaled bacilli, whereas the resistant strains require about 10 times as many bacilli for the formation of each tubercle.[10] If the animals are killed at the end of five weeks after inhalation of the same number of organisms, the ratio of bacteria inhaled to the number of tubercles formed provides a roughly quantitative estimate of the degree of resistance. Resistant rabbits may be made susceptible by the prolonged administration of corticotropin or cortisone.

The adrenal secretions of the suceptible (FC) and resistant (Race III) strains of rabbit were examined. In some instances the yields of blood were small enough to require the pooling of samples to provide sufficient material for analysis. As a result, all of the blood obtained from a given group of animals was treated as a single pool, and the data for such pools are shown in Figure 5. There is insufficient material for statistical treatment; hence the results must be regarded as suggestive rather than definitive.

The data suggest the following conclusions. First, both the susceptible and resistant strains of rabbit produce detectable amounts of hydrocortisone, in the controls, in contrast to our genetically undefined laboratory strain. Second, there is suggestive evidence that susceptible rabbits produce about twice as much hydrocortisone as do the resistant ones. This is especially interesting because the resistant strains become much more susceptible to tuberculosis if they are treated with cortisone or corticotropin. Third, the infected susceptible animals do not increase their adrenal steroid output significantly over control levels, although the tuberculous resistant animals increase their secretion of both hydrocortisone and corticosterone. Fourth, corticotropin acts quite differently from tuberculosis in terms of the adrenal secretory product. Although the infection may lead to greater total steroid output than follows one week of treatment with corticotropin, the relative and absolute amounts of hydrocortisone that are secreted after the use of corti-

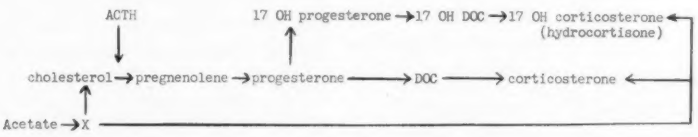

Figure 4.

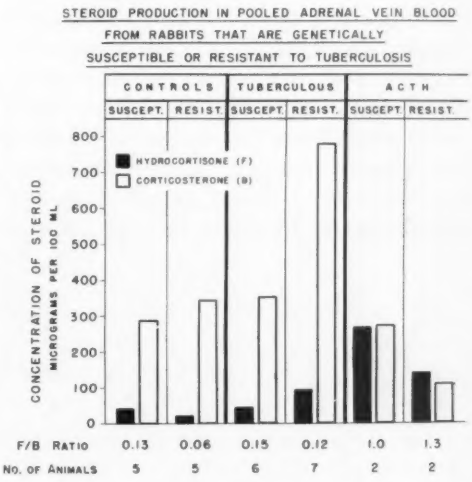

Figure 5.

cotropin are greater than the amounts that follow the stimulation of infection. Whether this indicates that tuberculosis in some way alters the capacity of the adrenal cortex to respond remains to be seen. These animals are bred with difficulty; hence the data must accumulate slowly.

SUMMARY

The biologic problem that is presented is that hydrocortisone and corticosterone, which differ by one hydroxyl grouping, have qualitatively similar metabolic effects and similar efficacy in the treatment of adrenal insufficiency but exert different effects on mechanisms of resistance to infection. These may be only quantitative; the difference is nevertheless striking. Hydrocortisone decreases resistance to infection and depresses immune responses; corticosterone in the same dosages does not have these effects. Corticotropin may cause the adrenal secretion of rabbits to alter markedly so that animals which usually secrete corticosterone as the predominant adrenal steroid may become predominantly hydrocortisone secretors. Changes in the immune status of the animals may be demonstrated after treatment with different amounts of corticotropin, and these changes agree with those that would be predicted on the basis of the alteration in the nature of the adrenal secretory product. Differences in the ratio of secretion of corticosterone and hydrocortisone may be induced by a variety of stimuli, but the response in terms of total quantity as well as type of steroid is highly variable and is as yet not predictable. There is suggestive evidence that genetic influences on steroidogenesis may correlate to some degree with genetic differences in resistance to tuberculosis; genetically susceptible animals secrete about twice as much hydrocortisone as do genetically resistant rabbits. Corticotropin-treated rabbits may, despite smaller total steroidal secretion, secrete larger amounts of hydrocortisone than are secreted by genetically resistant rabbits infected with tubercle bacilli.

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Shock Associated with Bacteremia

Review of Thirty-Five Cases

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The complications of hypotension and shock have been reported several times in a few patients with bacteremia.* However, most reports on shock and bacteremia have given little emphasis to their association. Hypotension is frequent in typhoid fever, peritonitis, cholera, bacillary dysentery, gas gangrene, diphtheria, meningococcemia, and several rickettsial diseases. Various factors such as prostration, dehydration, fever, cardiac failure, and adrenal insufficiency have been assumed to be responsible for the hypotension, but the precise mechanism of shock in infections is far from clear.[3]

The hypotension that accompanies bacteremia often goes unrecognized because the signs and symptoms of bacteremia do not suggest its presence. The patient often is alert and at first may have suffused, warm, dry skin. Moreover, signs of shock such as weakness, thirst, sweating, tachycardia, and lethargy may be attributed to the infection per se. One must be alert to detect hypotension during infection, and infection may be overlooked in a patient with shock; yet bacteremia has been one of the most frequent causes of shock in this hospital.

This is a report of 35 patients observed at the Minneapolis Veterans Administration Hospital during the past seven years and found to have shock associated with bacteremia. The purpose of this paper is to emphasize the clinical features, serious implications, and some therapeutic considerations of shock accompanying bacteremia.

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* References 1-8.

METHODS AND MATERIALS

The records of 100 patients with bacteremia were analyzed. Thirty-five patients had hypotension, with several systolic blood pressure readings under 95 mm. Hg. These 35 cases had bacterial growth in both broth and nutrient agar cultures of the blood (20 cases) or only in the broth cultures (15 cases). Sixty-five of the one hundred patients had no recorded hypotension during the period of bacteremia. Several typical instances of shock and infection but negative blood cultures were omitted. One case with bacteremia and shock but normal blood pressure also was omitted. Patients with subacute bacterial endocarditis, hemorrhage, and agonal bacteremia were arbitrarily excluded from the study because decreased blood volume, cardiac valvular defects, and preterminal disease states may produce marked hemodynamic alterations.

RESULTS

The data recorded in the Table reveal that shock with bacteremia occurred oftenest in persons over 45 years of age. The average age of the patients was 61 years, presumably because older men more often have foci of infection leading to bacteremia. There were 18 deaths among the 35 patients with shock, the mortality rate being 51%. The most frequent underlying disease was a malignant neoplasm, and 7 out of 11 patients with malignant disease died shortly after their episode of bacteremia and shock. There were two patients with multiple myeloma and bacteremia resulting in shock. Abnormal gamma globulins and deficient antibody production probably were responsible for the bacteremia.[9] There were 10 patients with definite coronary arteriosclerosis, and only 4 died as a result of shock with their bacteremia.

The genitourinary tract was the most frequent source of bacteremia leading to shock. Of the 15 patients, 13 had had recent urethral

Clinical Data for Thirty-Five Patients with Bacteremia and Shock

Patient	Age, Yr.	Diagnosis	Source of Bacteremia	Blood Culture (Col./Ml.)	Hypotension		Fever		Skin	Therapy *	Outcome
					Level, Mm. Hg	Duration	Maximum Temp., F	Duration			
1. K. J.	75	Prostatic hypertrophy	Urethral catheter	A. aerogenes (5)	50/0	12 hr.	105.8	24 hr.	Cold, clammy	Pen, SM	Death in 24 hr.
2. E. M.	60	Carcinoma, lung	Cystoscopy	Paracolon, E. coli (624)	55/45	5 days	104	5 days	Warm, dry	Pen, DHSM, Eph, Neo-Syn, Epin	Improved temporarily
3. N. B.	62	Urethral stricture	Urethral dilatation	Staph. albus (12)	255/145→ 94/70	2 hr.	103	24 hr.	Flushed	Pen, CT, SM	Recovered
4. A. T.	54	Urethral stricture	Urethral dilatation	A. aerogenes	70/50	3 days	101.4	3 days	Flushed	Pen, CT, SM	Recovered
5. J. Mc.	66	Carcinoma, bladder	Cystogram	E. coli, P. mirabilis, diphtheroids (300)	66/40	24 hr.	98	.....	Pale, warm, dry	OT	Death in 7 days; BUN 118 mg./100 cc.
6. E. D.	63	Perinephric abscess	Perinephric abscess	P. morgani	82/48	25 days	101	25 days	Pale, cold, moist	Pen, CT, SM Bl	Died 24 hr. postop.
7. W. C.	60	Carcinoma, prostate	Cystogram	Hem. Staph. aureus, coag.+ (11)	92/56	4 hr.	104	2 days	Pale, cold, moist	Digit, Chl	Recovered
8. G. R.	77	Tuberculosis, wrist	Retrograde pyelogram	P. rettgeri	80/50	4 days	102.6	7 days	Flushed	Pen, CT, T Chl, *l*-A, Bl	Recovered
9. O. F.	63	Renal calculi	Ureteral calculus	Proteus	60/40	18 days	101	6 days	Cyanosed, cold, moist	OT, Chl, Pen, F, M, Eph	Slow recovery
10. M. M.	84	Prostatic hypertrophy	Urethral catheter	E. coli	60/0	6 days	102	24 hr.	.....	T, Pen, SM, F, M	Recovered
11. J. H.	62	Prostatic hypertrophy	(1) Retrograde pyelogram	Paracolon	90/60	1 hr.	98	.....	Normal	T, Pen, Digit	Rapid recovery
			(2) Cystostomy	Paracolon	196/90	.....	103.6	11 days	Flushed	Pen, Chl	Recovered
			(3) Prostatectomy	Paracolon	58/0	1½ hr.	103.6	6 hr.	Flushed	T, Pen, CT, *l*-A, Bl	Recovered
12. F. O'F.	56	Prostatic abscess	Urethral catheter	Proteus	64/0	72 hr.	104	24 hr.	Pale, cold, moist	OT, Pen, E, F, SM, T, Chl, V, *l*-A, D, Bl	Recovered
13. H. B.	67	Prostatic hypertrophy	Prostatectomy	Proteus (3)	60/40	6½ hr.	105	10 days	.....	T, Pen, SM, Chl, F, D, Bl *l*-A, M	Recovered
14. W. C.	65	Carcinoma, prostate	Prostatectomy	Paracolon (3)	80/60	4 hr.	100	4 hr.	Pale, cold, moist	T, CT, V, M, Bl	Recovered
15. W. H.	77	Prostatic hypertrophy	Prostatectomy	A. aerogenes, Paracolon	68/0	24 hr.	99	.....	Pale, cold, cyanosed	CT, Pen, T, Chl, Bl, V, M	Recovered
16. C. S.	24	Infected laceration	Infected laceration	Staph. aureus (80)	86/40	2 days	105	5 days	Flushed	Pen, CT	Recovered
17. B. M.	58	Aplastic anemia	Pyoderma	Staph. aureus (176)	75/42	24 hr.	104	13 days	Pale, cold, moist	Pen, SM, E, OT, *l*-A, Bl, ACTH, C, ACE	Death in 13 days

18. E. B.	62	Carcinoma, rectum	Postoperative wound abscess	Staph. aureus (3) P. mirabilis	60/20	24 hr.	105	3 days	.....	Pen, SM, OT, CT, Bl, Pl	Death in 3 days; BUN 124 mg./100 cc.
19. F. M.	58	Abscess, thigh	Abscess, thigh	Strep. pyogenes (32)	84/44	24 hr.	104	8 days	.....	Pen, CT	Recovered
20. H. L.	57	Acute bacterial endocarditis	Diabetic gangrene	β-hem. Strep. (7)	70/0	3 days	106.2	25 days	Flushed	Pen, OT, Pl, D	Improved temporarily
21. L. N.	59	Common-duct stone	Common-duct stone	E. coli (33)	60/30	24 hr.	105	5 days	Flushed	Pen, CT, surgery, Bl	Recovered
22. O. F.	55	Empyema, gall bladder	Gall bladder	Paracolon	(1) 68/40 (2) 0/0→ 85/55	14 hr. 24 hr.	102.6	4 days	.....	Pen, OT, CT, Bl	Died with hypotensive relapse
23. P. B.	65	Empyema, gall bladder	Gall bladder	Paracolon (5)	60/40	8 days	102.6	4 days	.....	Pen, OT, CT, Bl	Death in 21 days; BUN 210 mg./100 cc.
24. O. A.	44	Cirrhosis, cholangitis	Bile ducts	E. coli (800)	74/50	24 hr.	103	3 days	.....	Pen	Death in 3 days
25. A. F.	57	Lobar pneumonia	Pneumonia	D. pneumoniae, I (8)	88/60	24 hr.	103	6 days	Pale	Pen, OT	Recovered
26. J. A.	55	Lobar pneumonia	Pneumonia	D. pneumoniae, I	80/60	24 hr.	103	24 hr.	Pale, cold, moist	Pen	Death in 24 hr.
27. A. R.	62	Lobar pneumonia	Pneumonia	K. pneumoniae (0.5)	92/80	5 hr.	.....	.....	.....	Pen	Death in 5 hr.
28. J. Ol.	65	Carcinoma, stomach	Postoperative peritonitis	Paracolon	54/0	7 days	103	7 days	Pale, cold, moist	Pen, OT, Bl, Pl, Eph	Death in 7 days; BUN 83 mg./100 cc.
29. G. J.	60	Carcinoma, bile ducts	Postoperative peritonitis	Paracolon (13)	82/52	36 hr.	104	3 days	Cyanosed, cold, moist	Pen, SM, OT, T, V, *l*-A, Bl, Pl, Digit, ACE	Died 3 days postop.
30. J. Ob.	60	Duodenal ulcer	Postoperative peritonitis	P. rettgeri (610)	60/40	14 days	104	4 days	.....	Pen, SM, T, Chl, Bl, Pl	Death in 14 days with icterus
31. P. H.	73	Carcinoma, colon	I.V. polyethylene tubing	Staph. aureus (434)	80/0	4 days	104.5	4 days	Dusky	Pen, OT, SM, STH, Bl, Pl, Digit	Death in 4 days
32. P. L.	64	Carcinoma, thyroid	I.V. dextrose and tubing	Staph. aureus	54/0	6 hr.	98	.....	Pale, cold, clammy	*l*-A, Bl, Pl, ACE	Recovered
33. L. T.	65	Multiple myeloma	Pharynx	(1) N. catarrhalis,	64/30	4 days	101.4	16 hr.	Pale, warm, moist	Pen, SM, T, M	Recovered
				(2) D. pneumoniae, XX	60/40	18 hr.	104	24 hr.	Flushed	Pen, M	Recovered
34. C. H.	62	Myotonia dystrophica, multiple myeloma	X-ray therapy?	Paracolon	50/35	5 hr.	105	8 hr.	Pale, warm, moist	Pen, SM, OT, *l*-A, Bl, C	Died in 8 hr.
35. H. V.	47	Acute gastroenteritis	Intestine	Hem. Staph. aureus, coag.+	78/64	3 hr.	103	4 days	Pale, cold, moist	Pen, Sm, CT, D, Bl	Died with icterus, anuria in 8 days

* Pen, penicillin; SM, streptomycin; DHSM, dihydrostreptomycin; T, tetracycline; CT, chlortetracycline (Aureomycin); OT, oxytetracycline (Terramycin); Chl, chloramphenicol; F, Nitrofurantoin (Furadantin); E, erythromycin; STH, Sulfathalidine; Bl, whole bank blood; D, 6% dextran; Pl, human plasma; Eph, ephedrine; Neosyn, phenylephrine (Neo-Synephrine); V, methoxamine (Vasoxyl); M, metaraminol (Aramine); Epin, epinephrine; *l*-A, levarterenol (Levophed); C, cortisone; ACTH, corticotropin; ACE, adrenal cortex extract; Digit, digitalis.

instrumentation or surgery and 2 had abscesses. Cutaneous abscesses or pyoderma accounted for five cases. Four patients had an acute biliary tract infection. The bacteremia in the remaining patients was the result of pneumonia (three), peritonitis (three), contaminated dextrose solution and polyethylene tubing used for intravenous administration (two), multiple myeloma (two), and acute gastroenteritis (one).

The bacteria isolated from the blood in the 35 cases with shock (Table) were Paracolobactrum sp. (nine), Proteus sp. (eight), Micrococcus pyogenes var. aureus (eight), Escherichia coli (five), Aerobacter aerogenes (three), Diplococcus pneumoniae (three), Streptococcus pyogenes (two), Klebsiella pneumoniae (one), and Neisseria catarrhalis (one). Thus Gram-positive cocci were the responsible agent in 34% and Gram-negative bacilli, in 66% of the episodes of shock. The Gram-negative bacilli were mostly enteric organisms. Five patients had more than one type of bacteria in their blood cultures. Two patients had more than one episode of bacteremia with shock. The number of organisms in the blood showed a moderate correlation with the occurrence and severity of shock. In 20 patients, quantitative cultures indicated that the number of bacteria ranged from 0.5 to 800 per milliliter of blood (mean, 158). All of the six patients with more than 100 bacteria per milliliter of blood died after the onset of hypotension, while only 41% died following lesser bacteremia. Strangely enough, several other patients with up to 300 similar bacteria per milliliter of blood suffered no shock.

The average blood leucocyte count was 17,000 per cubic millimeter. Neutrophiles constituted from 4% to 97% of the total leucocytes (mean, 83%). A neutrophilic leucocytosis occurred in all but 10 patients. Eight of these ten patients died.

The onset of bacteremia in nearly all the hypotensive patients was abrupt and was marked by a shaking chill. A fall in blood pressure was noted within several minutes to a few hours, the systolic blood pressure declining to less than 95 mm. Hg in all instances and to 80 mm. Hg or below in 27 patients (Table). The duration of the hypotension varied from 2 hours to 25 days (mean, 3.2 days). Following the chill and preceding the fall in blood pressure there was an abrupt rise in body temperature in all but three patients (Table). In one other patient the temperature was not recorded. The average duration of fever was six days.

The condition of the skin was recorded at the onset of hypotension in 26 patients (Table). In only 58% was the skin of the extremities pale, cold, and moist. These patients tended to have clouded sensorium with apathy and listlessness. Their pulse was weak and thready, with the rate ranging from 60 to 140 per minute (mean, 113). In 42% of the patients the skin was warm and dry or flushed. These patients were bright, alert, and active. Their pulse was full and bounding, with a rate of 75 to 110 per minute (mean, 96). It should be noted that several of the latter cases soon developed a more typical picture of shock with peripheral vasoconstriction.

Nausea, vomiting, and diarrhea were uncommon. None of the patients had melena, hematemesis, or hematuria. Terminal oliguria and uremia were noted in six hypotensive patients, and two patients became jaundiced shortly before their death. Two patients had numerous petechiae and ecchymoses. In one case of staphylococcic bacteremia (Patient 17, Table) each of the numerous petechiae had a minute abscess at its center.

The treatment given for the bacteremia and hypotension has been listed in the Table and included chemotherapy, plasma volume expanders, vasconstrictor drugs, steroid hormones, and digitalis. In most instances several antibiotics were employed, although the selection was not always appropriate. Until recent years the therapy was not uniformly based on in vitro antibiotic-susceptibility tests, in part because of the rapid progress of the shock to death and mistaken clinical evaluation (Patients 24 and 27, Table). Susceptibility tests were done by a broth-dilution method in 24 of the 35 cases. In 16 cases the antibiotics used seemed effective in vitro, but in 8 cases

the bacteria were resistant to the drugs given. The organisms isolated from 11 patients were not tested, but the choice of antibiotics seemed correct in 7. The mortality rate was only 30% in 23 patients given appropriate chemotherapy, and it was 91% in 12 receiving inappropriate antibiotics.

Whole blood, plasma, or dextran was given to 19 patients and did not seem to improve the outcome (11 deaths). Parenteral vasoconstrictor drugs such as ephedrine, phenylephrine (Neo-Synephrine), epinephrine, methoxamine (Vasoxyl), metaraminol (Aramine), and levarterenol (Levophed) produced a definite but often unsustained rise in the blood pressure of 14 patients. Continuous intravenous levarterenol was the most effective drug, but the increase in blood pressure was only transient. Intramuscular metaraminol had more prolonged but lesser activity. The mortality rate was 57% in the 21 patients receiving no vasoconstrictor drugs and only 36% in the 14 patients given these medications. There were no deaths among six patients on metaraminol and only three deaths among seven patients given levarterenol, although these drugs at first were reserved for very sick patients.

Corticotropin (ACTH), cortisone, or adrenal cortex extract was given to four patients (Patients 17, 29, 32, and 34; Table). Improvement occurred in two but could not be attributed solely to this therapy. Digitalis was given to four patients and was helpful in three with rapid auricular fibrillation developing after the onset of hypotension. Delayed cholecystectomy and removal of a common bile duct stone contributed much to the final good result in one case (Patient 21, Table).

Sixteen of the hypotensive patients died soon after the development of shock. Two additional patients (Patients 2 and 20, Table) improved temporarily but relapsed and died several days later. This high mortality rate (51%) contrasted with a death rate of only 23% in 65 patients treated for similar bacteremia without hypotension.

Necropsy was performed in 14 cases and revealed evidence of heart disease in 7. The pathological findings included focal myocarditis (one), primary "amyloidosis" of the coronary arteries (one), petechial myocardial hemorrhages (one), and coronary arteriosclerosis with myocardial fibrosis (four). Thirteen of fifteen patients who survived the bacteremia and shock showed electrocardiographic abnormalities during their illnesses. These consisted of nonspecific T-wave changes in nine and auricular arrhythmias in four patients. One patient had a transient right ventricular strain pattern and ventricular tachycardia. Autopsy also revealed numerous subcutaneous, serosal, and mucosal hemorrhages and petechiae in three patients. Of five paients with terminal oliguria and uremia, examination of the kidneys showed hydronephrosis in two, microscopic cortical abscesses in two, and hydropic degeneration of the proximal convoluted tubules with protein and hemoglobin casts in their lumina in three. Two cases with late jaundice showed necrosis of hepatic cells in the center of the lobules. The adrenal glands were abnormal in only one patient (Patient 29, Table). The later had hemorrhages and necrosis in the cortex of both adrenal glands, as well as widespread petechiae, peritonitis, and pancreatitis following pancreatic resection for carcinoma.

COMMENT

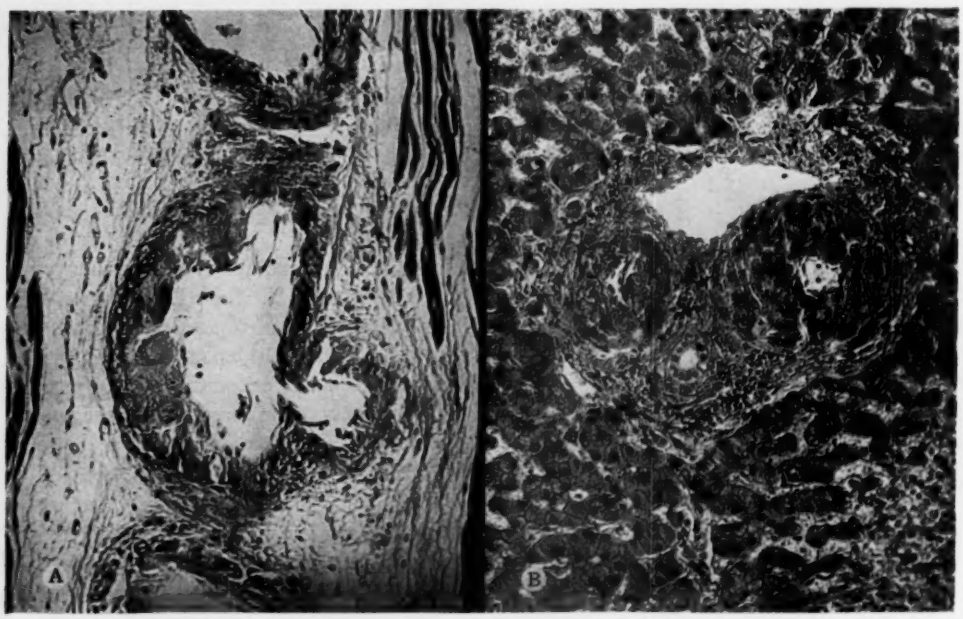
It is likely that shock in most infections is caused by the bacterial endotoxins (polysaccharides and phospholipid-polysaccharide-protein complexes) which are pyrogenic.† Yet in patients with bacteremia the fever and blood pressure often show little correlation. The factors which increase susceptibility to shock during bacteremia are largely unknown. It is accepted that adrenal insufficiency, liver disease, anemia, malnutrition, and hypovolemia predispose patients to hypotension during infection.

Carcinoma and coronary arteriosclerosis were frequent among the patients in the present study. The genitourinary tract was the source of the bacteremia in about 40% of the patients. Gram-negative enteric bacilli were the cause of the hypotension in two-thirds of

† References 4, 29, and 30.

the cases. Although there was a considerable variation, the mean pour-plate count of bacteria in the blood of the hypotensive patients was high (158 per milliliter). Neutrophilic leucocytosis was frequent. Death occurred in 8 of 10 hypotensive patients who had leucopenia.

Although hypotension may be brief and benign, sustained low blood pressure and shock often are fatal complications of bacteremia. Every patient in the present series was seriously ill, and 18 of the 35 patients onary arteries in one patient (Patient 22, Table). Identical hyaline material was found throughout the walls of arterioles and small arteries in all the organs (Fig., *A* and *B*). The substance stained rather poorly with methyl violet. The lesions were very similar to those seen in the coronary arteries of rabbits challenged with streptococci and an endotoxin from Gram-negative bacteria.[11] Two other patients had numerous petechiae in the myocardium; emboli or thrombi were not found in the coronary blood vessels.



A, coronary artery showing hyaline "amyloid" deposits in its wall. *B*, portal area in the liver containing blood vessels with a large amount of fibrinoid material throughout their walls. Hematoxylin and eosin; reduced about 3/7 from mag. × 90. This patient died after two episodes of shock caused by a paracolon bacteremia arising from an empyema of the gall bladder. The hyaline material stained strongly with the periodic acid-Schiff stain.

died. Half of the 14 patients studied at necropsy had evidence of cardiac disease, and electrocardiographic abnormalities were present in most of those who survived. The EKG changes often were transient. Hypotension with bacteremia may be a grave complication for people with coronary arteriosclerosis. In only three of the fourteen necropsies were cardiac lesions found which might be ascribed to the bacteremia. The most unusual finding was atypical "amyloid" deposits in the cor-

The level of the arterial blood pressure is determined by the cardiac output and total peripheral vascular resistance. The dynamics of the hypotension and shock associated with bacteremia have been studied extensively.‡ Perhaps the first study was that of Romberg and his associates, in 1899.[14] The blood pressure usually rises with a chill and quickly falls to normal or below as the temperature

‡ References 3, 4, 10, 12-20, and 38.

rises. Early in the fever of infection there is dilatation of the peripheral vascular bed, increased peripheral circulation, and increased cardiac output.§ Eleven of twenty-six patients in the present series showed evidence of this situation when hypotension was first noted; their skin was warm, dry, and flushed; their pulse was full and sensorium, alert.

Shortly after the onset of hypotension, there is peripheral vasodilatation, with pooling of blood in the periphery,[18] increased arteriovenous oxygen difference,‖ diminished venous return,¶ decreased right and left auricular pressure,# and falling cardiac output.* Peripheral vasoconstriction sets in but is often insufficient to maintain the blood pressure, in spite of rising peripheral resistance, because of persistently low cardiac output.†

There are few objective data to show that the myocardium is injured.‡ In the absence of auricular fibrillation, digitalis is of no benefit.[1] There is little early hemoconcentration, and the circulating blood volume falls very little if at all.§ However, recent experimental data indicate that a small decrease in circulating blood volume after injection of a bacterial toxin may lead to a marked decline in cardiac output and blood pressure.[10]

Bacterial infection and hypotension may have a synergistic effect. Experimental animals with shock induced by bacterial toxins or other agents are more susceptible to bacterial infections.‖ Dogs bled to shock level recover oftener if pretreated with chlortetracycline or neomycin.¶ Peritonitis has been found to be an important factor leading to intractable hypotension among human battle casualties.[26] Experimental work has suggested that bacterial infections play an important role in the shock following crush injuries.#

Shock associated with meningococcal infections (Waterhouse-Friderichsen syndrome) has been attributed to hemorrhage in the adrenal glands resulting in adrenal insufficiency. Autopsy in 14 fatal cases in the present series showed hemorrhage and necrosis in the adrenal glands in only 1. Likewise, dogs given fatal doses of meningococcal toxin or Gram-negative bacteria intravenously show only capillary engorgement or occasional petechial hemorrhages in the adrenals; petechiae are seen oftener in the serous membranes, lungs, myocardium, and intestinal mucosa.[10] The adrenal hemorrhages may be only a manifestation of widespread vascular damage. Adrenal insufficiency has not been proved to play a frequent role in any form of bacteremic shock.

An ideal program for the treatment of bacterial shock is not yet available. There are several reports in the literature of successful therapy of the Waterhouse-Friderichsen syndrome with adrenal cortex extract, and a few recoveries also have been ascribed to the use of cortisone and hydrocortisone. Corticotropin and cortisone in conjunction with antibiotics have been found to be helpful in severe infections; they suppress fever, neutrophilic leucocytosis, and other toxic signs.* Four patients in the present series were given these agents or adrenal cortex extract, and only one recovered. The possible beneficial effects upon the circulation are difficult to assess. Experiments in dogs have showed that large doses of cortisone do not prevent hypotension and shock caused by a large amount of meningococcal toxin.[10]

Early and effective therapy with antibacterial agents is an essential requirement. The great value of a proper selection of antibiotics guided by antibacterial susceptibility tests is shown by the present study. Almost all patients given ineffective drugs died, but the mortality rate was only 30% in those whose antibiotics were well chosen. Often the chemotherapy must include more than one anti-

§ References 1, 13, and 19.

‖ References 3, 4, 16, and 18.

¶ References 3 and 16.

References 3, 10, and 16.

* References 3, 4, 10, 13, 15, 16, 18, and 38.

† References 12 and 18.

‡ References 3, 12, and 18.

§ References 3, 4, 10, 12, 16, 18, 21, and 22.

‖ References 23 and 24.

¶ References 21 and 25.

References 17, 19, 27, and 28.

* References 31-33.

biotic agent, at least until the identity and in vitro antibiotic susceptibility spectrum of the responsible bacteria are determined. It seems logical to combine a bactericidal antibiotic such as penicillin, erythromycin, or streptomycin with a broad-spectrum antibiotic such as chloramphenicol, tetracycline, chlortetracycline (Aureomycin), or oxytetracycline (Terramycin). The danger of drug antagonism in such situations is not great.† If a staphylococcic infection seems likely, the use of erythromycin, chloramphenicol, or bacitracin is indicated, because many strains are now penicillin-resistant. At first parenteral administration of the antibiotics is preferable, since gastrointestinal absorption is not reliable in patients with shock. Rapid sterilization of the blood and infected foci is sought. Therapy with antibiotics has lowered the mortality of many common infectious diseases, but antibiotics alone often will not suffice when shock occurs. In fact the use of a large dose of an effective antibiotic in an infection caused by a Gram-negative bacterium may lead to hypotension.[35] The fall in blood pressure may be the result of rapid killing of the bacteria, with release of large amounts of bacterial endotoxin, i. e., a Jarisch-Herxheimer reaction (therapeutic paradox).

Antitoxin should be administered early and in adequate doses in all cases of diphtheria, tetanus, and gas gangrene. Antitoxin also may be useful in staphylococcic and meningococcal infections with hypotension; unfortunately, such antitoxic sera are no longer available.

Although hemoconcentration and decline in circulating blood volume may not be great, experimental data indicate that small reductions in blood volume may lower blood pressure markedly after the onset of hypotension caused by a bacterial endotoxin.[10] It might be helpful to give a moderate amount (500 to 1000 ml.) of whole blood, pooled plasma, or other plasma volume expander (dextran). A sustained rise in blood pressure was observed in several patients given such therapy, but the mortality rate was not reduced. A marked increase in auricular filling pressure and cardiac output has been observed after administration of dextran in large doses in dogs.[10] The mean blood pressure increased moderately but did not return to normal. Excessively large and rapid transfusions may lead to pulmonary edema and are not desirable. One should not attempt to restore the blood pressure to normal by the use of plasma volume expanders alone.[10]

Since there is ample evidence of pooling of blood in the periphery in spite of physiologic vasoconstriction in the skin of the extremities, vasoconstrictor drugs have been used extensively. Most of these drugs will effectively raise the blood pressure transiently, but in patients with severe shock response to the drugs often declines rapidly (tachyphyllaxis). The blood pressure may fall whenever the dose is reduced, even though the infection is controlled. The most effective drug is levarterenol.‡ In seven patients in the present series, levarterenol produced a marked and continued elevation in blood pressure when given without interruption in relatively large doses. The dose often was difficult to control, and some care was necessary to avoid pulmonary edema, since levarterenol must be given in a constant intravenous infusion. In a few cases the urine output was low while levarterenol was given, in spite of an adequate blood pressure. This may have been the result of excessive renal vasoconstriction. Experimental studies have shown that levarterenol produces a marked but transient increase in systemic blood pressure accompanied by very little rise in cardiac output.[10] Metaraminol proved very useful in six patients. Though less effective than levarterenol, this drug produced less precipitous and more prolonged elevations in blood pressure. Another advantage was the fact that it could be given intramuscularly and did not have to be injected continuously. Thus it was easier to give and often resulted in less violent fluctuations of blood pressure. Vasoconstrictor drugs were required in most patients for only a few days. In one case (Patient 9, Table) metaraminol and other pressor drugs were required in large but diminishing doses for three weeks before

† References 7, 8, and 34.

‡ References 6, 8, 36, and 37.

the blood pressure remained stable. Both levarterenol and metaraminol seemed to aid in reducing the mortality rate.

SUMMARY AND CONCLUSIONS

Thirty-five patients with associated bacteremia and shock are reported. The mortality rate was 51%.

The most frequent sources of bacteremia were the genitourinary tract, cutaneous suppuration, the biliary tract, peritonitis, and lobar pneumonia. The most frequent causal bacteria were Paracolobactrum sp., Proteus sp., M. pyogenes var. aureus, E. coli, Aerobacter (Klebsiella) sp., and D. pneumoniae, in that order.

Typical signs of shock were present at the onset of the hypotension in 15 of 26 patients. In the others the hypotension was masked by flushing of the skin, bounding pulse, and other circulatory changes caused by the infection; shock appeared late in these patients.

Prompt use of effective antibiotics controlled the bacteremia, but shock frequently remained unchanged and often led to death. Blood and plasma transfusions often raised the blood pressure level somewhat but did not reduce the fatality rate. Vasoconstrictor drugs given in large doses were very useful in restoring the blood pressure; levarterenol and metaraminol were most effective. Steroid hormones did not seem to lessen the shock.

Shock and death were not caused by adrenal insufficiency. Seven of the fourteen patients studied at necropsy showed signs of cardiac disease which may have contributed to the fatal outcome. Widespread damage to small blood vessels and petechiae was often found.

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Arteriovenous Aneurysms of the Innominate Vessels

Review of the Literature and Report of One Case

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The rarity of reported cases of arteriovenous aneurysm of the innominate artery is amazing. This is explained by the fact that the etiology is usually traumatic and that trauma sufficient to penetrate the thorax and lacerate the innominate artery is usually fatal.

Exploration of the "Quarterly Cumulative Index Medicus" and the "Index Medicus" in their entirety, a search of cross references and collateral reading back to Hunter's monograph in 1757,[1] and checking numerous case reports has yielded but two cases.*

Twelve series of reported cases of aneurysm were studied † (Table). Various modes of selection were employed in these series, i. e., surgical cases, traumatic aneurysms, radiographically studied cases, etc. Therefore the figures obtained do not represent the absolute incidence of aneurysms. The venerable analysis of aneurysms by Crisp, in 1947,[4] was the most extensive work. He collected 531 cases of aneurysm and reviewed a group of 364 at the London Museums. No instance of innominate arteriovenous aneurysm was mentioned.

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* References 2 and 3.

† References 4-17.

These series contain a total of 2198 aneurysms, including 834 arteriovenous aneurysms and 80 arterial innominate artery aneurysms. The two innominate arteriovenous fistulae of the innominate artery and vein mentioned in the Table are identical with those mentioned above.

Erich Lexer reported the first case, in 1934. A 24-year-old man received a stab wound with a knife in the "jugular" region of the right side of the neck. Healing was complicated by infection. Residual symptoms included dyspnea, palpitation, headache, and chronic purulent bronchitis and a continuous roaring in his head. Upon examination 13 months later the wound scar was seen. The apical dullness extended past the left midclavicular line. A continuous murmur was heard to the right of the upper sternum, with radiation down along the sternum and up into the neck. Blood pressure in the left arm was 115/50 mm. Hg and in the right arm, 135/60 mm. Hg. Fluoroscopy disclosed a generally enlarged heart but no evidence of aneurysm. The clinical diagnosis was arteriovenous aneurysm of the innominate artery and vein.

The prognosis was considered hopeless, and surgical correction was undertaken. This was preceded by practicing the surgical approach on a cadaver. The operation required three hours, using ether and positive pressure oxygen. The clavicles were cut through, two fingerbreadths from the sternoclavicular joints; the first and second costal cartilages were severed one fingerbreadth from the sternum; the sternum was transected (presumably about the level of the second rib), and the manubrium with its clavicular and costal stumps laid back (presumably in-

*Analysis of Series of Aneurysms**

	Aneurysms, No.	Arterial Aneurysms	A-V Aneurysms	Innominate Aneurysms	Arterial Innominate Aneurysms	A-V Innominate Aneurysms
Crisp [4] (1847)	551	551	?	20	20	0
	364	364	?	3	3	0
Callander [5] (1920)	447	0	447	0	0	0
Pemberton [6] (1928)	25	0	25	0	0	0
Parks [7] (1938)	3	3	0	3	3	0
Rundle [8] (1937)	3	3	0	3	3	0
Holman [9] (1940)	25	0	25	0	0	0
Matas [10] (1940)	243	179	68	0	0	0
Bigger [11] (1944)	29	15	14	0	0	0
Lindskog [12] (1946)	95	?	?	35	33	2 (2.3%)
Shumacker † (1946-1948)	364	119	245	0	0	0
Gay [16] (1953)	18	18	0	18	18	0
Winn [17] (1954)	31	18	13	0	0	0
	2198	1270	837	82	80	2

* The artery involved was invariably identified, but frequently the type of aneurysm was not stated.
† References 13-15.

feriorly). Subcutaneous capillaries and veins were distended and bled freely. The thyroid and internal mammary veins were distended. The internal mammary vessels on the right were ligated and cut. The thymus was removed. The aneurysmal sac filled and protruded with expiration. It was thin walled, of the size of a chicken egg, and had a palpable thrill. The clinical diagnosis was confirmed. Pressure on the innominate artery stopped the thrill and caused a temporary bradycardia. The jugular, subclavian, and innominate veins were clamped distal to the sac, and the innominate artery was clamped proximal to the sac. The innominate artery was opened; a thrombus was removed, and the arterial end of the arteriovenous fistula was identified. This opening was closed with sutures. A strip was removed from the dilated left innominate vein to reduce it to its normal caliber. The bone flap was closed with wire sutures; drains were inserted, and the tissues were closed.

The patient developed an infection postoperatively and died on the 18th postoperative day. Autopsy showed an abscess at the origin of the superior vena cava and an empyema on the right. The closure of the arterial end of the fistula and the plastic procedure on the left innominate vein were in good condition.

D. C. Elkins reported the second case, in 1945.[3] A 25-year-old man was stabbed with a pair of scissors in the right upper chest. A severe hemorrhage developed; deep shock and unconsciousness resulted. Transfusions brought about prompt improvement, and he was discharged from the hospital four days later with dyspnea as his sole complaint. Five months later a murmur was heard and he was hospitalized. Examination showed a small scar below the right clavicle and 1 in. lateral to the sternum. In this area one could hear a continuous murmur with systolic accentuation and a continuous thrill could be palpated. Pressure did not obliterate these. The murmur radiated over the anterior and posterior chest walls, the neck, and both shoulders. Blood pressure was 130/50 mm. Hg in the right arm and 140/40 mm. Hg in the left arm. Venous pressure was 210 cm. of water in the left arm and 220 cm. of water in the right arm. Roentgenogram indicated cardiac enlargement. A month's rest improved his condition and decreased the size of the heart.

He was operated upon 14 months after the time of injury. Superiosteal resection of the medial halves of the clavicles, resection of the medial 2 in. of the second right rib, division of the sterum, and resection of the right half of the manubrium were performed to obtain adequate exposure. The innominate artery was ligated proximally and distally. The right innominate vein and the internal mammary vein and artery were ligated and divided. The thymus was removed. The

fistula was found between the innominate artery and the junction of both innominate veins. The veins and the proximal portion of the artery were greatly dilated. With the ligation of the innominate vessels the pulse rate dropped from 84 per minute to 72 and the blood pressure rose from 136/60 to 156/100. To excise the sac would have required division of the innominate artery, both innominate veins, and the subclavian artery. This was not done because of the danger of cerebral edema. The sternum and the ribs were replaced, and the seven-hour operation was concluded.

Postoperatively a hematoma developed under the pectoral muscles. Circulation in the right extremity remained adequate. A month after operation the heart had returned to normal size; the venous pressure was 154 cm. of water on the left and 234 cm. on the right. Arm and shoulder function was normal. An examination five months after the operation showed that both murmur and thrill were absent.

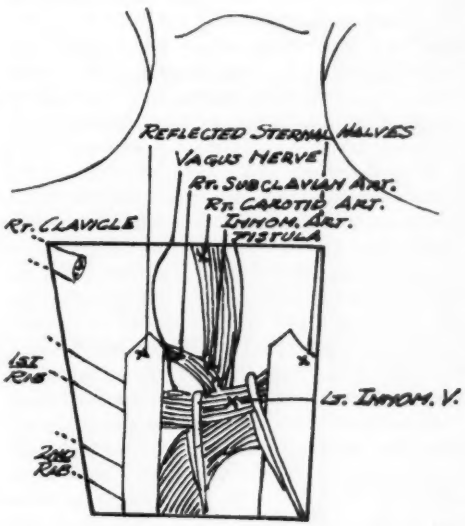
REPORT OF CASE

The patient was a 21-year-old Caucasian man. On June 10, 1952, in Korea, he received shell fragment wounds in the chest, abdomen, groin, and left arm. The latter three wounds were not very serious and were easily handled. Observation suggested the formation of a superior mediastinal hematoma, and this was evacuated. When strength and nutrition were improved, a thoracotomy with partial removal of the seventh rib was performed for the removal of shell fragments. He was discharged to limited duty on Nov. 3, 1952. He was asymptomatic except for a persistent "pulling sensation" over the right lateral chest wall, for which he reported on sick call. Examination disclosed a loud aortic murmur, and so he was hospitalized March 31, 1953.

Examination: He was well developed, strong, and healthy in appearance. Peripheral pulses were typically "water hammer" in quality. Pulse rate was 78 per minute. Blood pressure was 130/50 mm. Hg in both arms. No cyanosis or edema was noted. The trachea was in the midline and had no abnormal movements. There were three scars on the chest, two of them over the manubrium, the third following the course of the right seventh rib around the thorax. The area of cardiac dullness was of normal size. There was a rough, continuous murmur with systolic accentuation in the second right intercostal space to the right of the sternum, which radiated over the entire precordium, shoulders, neck, and back. "Pistol shot" sounds were heard in the groin bilaterally. Capillary pusations were visible in the fundi and in the nail beds.

Laboratory data: Complete blood cell count, urinalysis, serology, and sedimentation rate were normal. Electrocardiogram was normal.

Radiology: Roentgenograms and cardiac fluoroscopy disclosed the heart and great vessels to be of normal size, and the only abnormality found was a small piece of metal in the anterior superior mediastinum.



Operative site. Left innnominate vein retracted to show arteriovenous fistula.

Hospital course: The patient remained asymptomatic except for the "pulling sensation" over the right lateral chest wall. Circulation time with calcium gluconate was 11 seconds. Venous pressure in both cubital veins was 105 cm. of water. Under fluoroscopic control 25 cc. of sodium acetrizoate (Urokon sodium) was injected rapidly intravenously. The column of contrast media was noted to pass smoothly through the right innominate vein into the superior vena cava, the right heart, and out into the lung fields, without any abnormality being noted.

The patient was transferred to Valley Forge Army Hospital at Phoenixville, Pa. The clinical diagnosis was arteriovenous aneurysm between the innominate artery and an innominate vein. The patient was operated on May 29, 1953, under endo-

tracheal ether and oxygen. The skin was incised along the right clavicle to the jugular notch and then extended downward to the third interspace to the midclavicular line. A subperiosteal resection of the medial two-thirds of the clavicle was done. The internal mammary vessels on the right were ligated. The sternum was split from the jugular notch to the third interspace, and the halves were separated, thus obtaining adequate exposure. A marked thrill was palpable over the junction of the innominate veins. The pericardium was opened. The superior vena cava and the origin of the innominate artery were freed from scar tissue and their pericardial attachments. Pressure between the innominate artery and the left innominate vein obliterated the thrill, and a fistulous tract between them was exposed. Rubber tissue tapes were passed about the left innominate vein proximal and distal to the fistula. Traction on the innominate artery exposed the fistula just above its origin from the aortic arch. Dissection of scar tissue resulted in a small laceration of the posterior surface of the innominate artery which was repaired by interrupted sutures of 00000 black nonabsorbable (silk) suture material. A Satinsky clamp was placed in a lateral position on the innominate artery at the site of origin of the fistula. The fistulous tract was divided. Bleeding from the venous end was controlled by the tapes about the vein. The venous opening was everted with a running suture of 00000 black silk, and the arterial opening was treated similarly. Throughout the operation the innominate artery distal to the clamp maintained good pulsation. The clamp was removed. Soft tissue was interposed between the artery and vein. The sternum was reapproximated with periosteal sutures. A rubber tube drain was left in the right pleural space. The pericardium and tissue layers were closed anatomically. The total blood loss was 3,000 cc. and was replaced during the operation. The postoperative course was uneventful. The patient was returned to limited duty on July 21, 1953, and to full duty on Sept. 21, 1953.

The patient was last examined on May 26, 1954. He had no complaints. His heart was normal to auscultation and percussion. Electrocardiogram and roentgenogram of the chest were normal and unchanged. There was no clinical indication of increased venous pressure. Pulse rate was 72. The peripheral pulses were of normal tension. Blood pressure was 140/60 mm. Hg in both arms. An unexplained arteriolar spasm was noted in the left eye.

SUMMARY AND CONCLUSIONS

Arteriovenous aneurysm of the innominate vessels is a rare lesion.

Two such cases have been found in the literature. A third is reported.

The rarity of this lesion may be explained by the fact that a penetrating mediastinal injury which might cause this lesion is usually fatal.

The three cases had the following features in common:

1. Penetrating injury of the right upper chest resulting in internal hemorrhage

2. Latent period of 5 to 13 months between the original injury and recognition of an arteriovenous aneurysm

3. A continuous murmur and thrill in the right second intercostal space to the right of the sternum

4. Lack of the superior mediastinal syndrome, distinguishing this lesion from an arteriovenous aneurysm involving the aortic arch.

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Treatment in Internal Medicine

COMBINED HORMONAL-ANTIBIOTIC THERAPY IN PATIENTS WITH FULMINATING INFECTIONS

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TO HAVE practiced medicine during the past quarter century has been a privilege and an exciting experience. During that period, there has been a striking change of emphasis from tissue pathology to physiology and biochemistry. In association with this, therapeutic nihilism has been replaced by a dynamic and effective pharmacology. The two fields in which the most rapid advances in pharmacologic theory and practice have occurred are those of antibiosis and endocrinology.

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Those physicians who received their training and who practiced medicine in the period preceding the antibiotic era can well recall the feeling of inadequacy inspired by an average patient with Pneumococcus pneumonia and, to a much greater degree, by the patient with bacterial meningitis or Staphylococcus septicemia.

Following upon the initial demonstration of the effectiveness of sulfanilamide, increasingly potent chemotherapeutic and antibiotic agents became available at an amazing rate. As a result, the clinician may now approach the average patient suffering from a bacterial infection with a sense of confidence and adequacy.

In 1949, Dr. Hench and his associates made their initial reports relating to the effects of cortisone and corticotropin (ACTH) in patients with arthritis and other nonbacterial diseases characterized by widespread inflammation.[1] Later in that same year, Dr. Finland and his associates had occasion to observe the effect of corticotropin administration to a patient with a major bacterial disease characterized by an intensive inflammatory response, namely, Pneumococcus pneumonia.[2] The first patient so treated within 24 hours appeared clinically well, despite the fact that organisms could still be cultured from his blood stream. Subsequently the infection was eradicated, as the result of formation of specific antibodies. This observation impressed us as being of great importance.

Before proceeding further with a consideration of this type of observation, it may be well to review briefly the available knowledge concerning the relation of the adrenal cortex to infection. It has long been recognized that

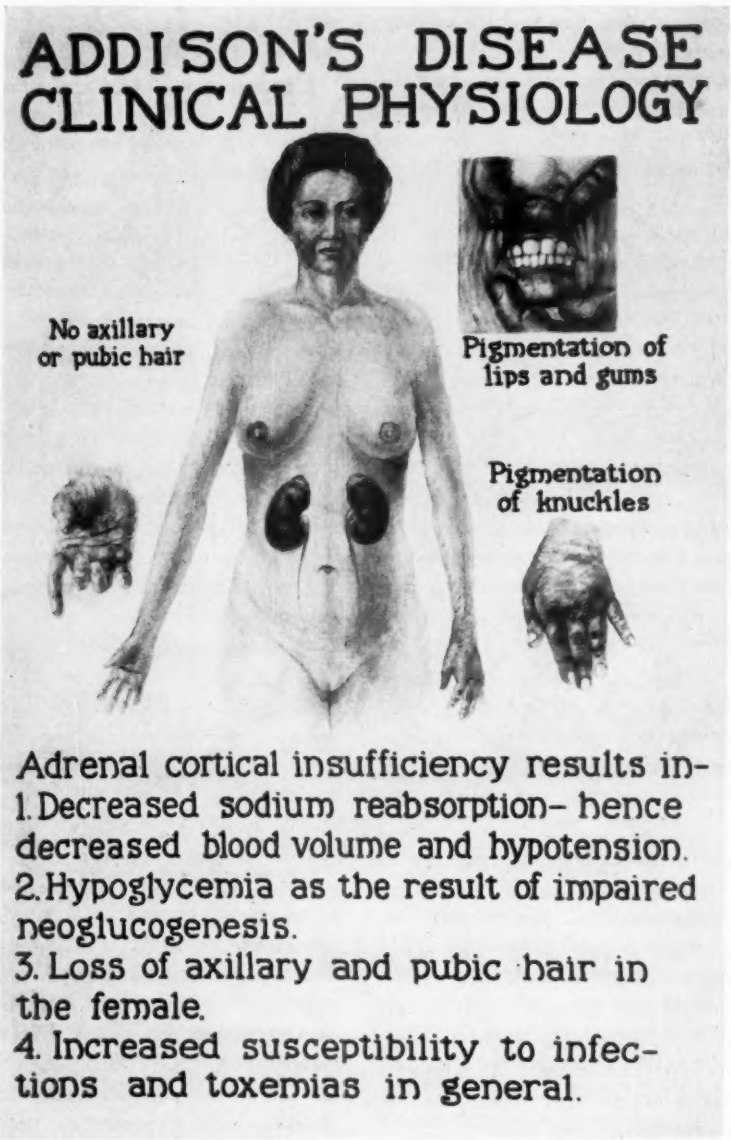
ADDISON'S DISEASE
CLINICAL PHYSIOLOGY
No axillary or pubic hair
Pigmentation of lips and gums
Pigmentation of knuckles
Adrenal cortical insufficiency results in-
1. Decreased sodium reabsorption- hence decreased blood volume and hypotension.
2. Hypoglycemia as the result of impaired neoglucogenesis.
3. Loss of axillary and pubic hair in the female.
4. Increased susceptibility to infections and toxemias in general.

Fig. 1.—The Addisonian patient before cortisone was notoriously hyporesistant to infection.

the Addisonian patient and the adrenalectomized animal are exquisitely sensitive to infection* (Fig. 1). The availability of desoxycorticosterone, a hormone-like material which essentially affects only salt and water metabolism, made for better stabilization of the Addisonian patient, but it in no way improved his ability to cope with infection. Very large amounts of whole adrenocortical extract frequently were required to enable such a patient to survive even a simple upper respiratory involvement. With the availability of cortisone and hydrocortisone, the entire picture changed. The Addisonian patient maintained with proper amounts of cortisone-like steroids is no more hypersensi-

* References 3-5.

tive to infection than is the average member of the population. When he acquires an infection, increased amounts of cortisone or hydrocortisone are required until the infection is controlled. From this type of observation, there would appear to be little question that adrenal steroids of the cortisone type are vitally implicated in the total process of resistance to disease. Recent experimental observations indicate that corticoids exert a significant protective effect against endotoxins elaborated by a variety of pathogens.†

Other observations exist, however, which indicate that administration of large amounts of corticoids can increase morbidity and mortality in experimental animals exposed to infectious organisms.‡ Also, there are reports in the literature indicating that in the human under certain circumstances corticoid administration can result in the dissemination of pulmonary tuberculosis and of other previously localized infections.[12]

Superficially, these two sets of observations would appear to be in conflict. However, if one investigates the known pharmacologic effects (as opposed to the physiologic effects) of the corticoids, the picture comes into focus.

At least three nonhormonal factors are concerned in the over-all picture of resistance to infectious disease:

1. The inflammatory reaction. This may be regarded as the first line of defense, tending to keep an organism localized until the production of specific immune bodies has gathered sufficient momentum. Inflammation is profoundly inhibited by pharmacologic amounts of corticoids (see below).

2. The production of specific immune bodies. These overwhelm the invading organisms and/or neutralize toxins produced by the organism, assuming that the inflammatory response has enabled the subject to survive the initial onslaught. This type of protection may be temporary or permanent. There is no evidence that corticoids, properly administered to human subjects, interfere with antibody formation (see below).

3. Antibiotics. If one were of a philosophical turn of mind, he might wonder why the Master Architect had not incorporated within us the ability to produce our own antibiotics as well as, or instead of, specific antibodies. To this, as to a great multitude of other philosophical questions, there is no readily available answer. As the result of the keen observation of men such as the late Professor Fleming, we have available to us agents which are relatively nontoxic to the host but which inhibit or destroy the majority of common and some uncommon nonviral infectious organisms. So efficient are these agents that both the inflammatory reaction and the production of specific immune bodies become of much less importance in determining whether a given individual shall survive the onslaught of infectious agents.

However, despite the efficacy of antibiotics, in any large hospital one still sees patients who, as the result of late diagnosis, poor constitutional status, or unusually virulent infections, succumb to infectious diseases. In the Alameda County Hospitals, as in most county hospitals, one sees a significant number of patients suffering from generalized peritonitis, meningococcemia, and other infections, who are admitted in a near-moribund condition. With Dr. Finland's observations in mind, in 1950 we decided to embark upon a program of combined hormonal-antibiotic therapy in such patients. This therapy was based upon the working hypothesis that the corticoids in some way exert a nonspecific antitoxic effect, protecting the cells of the host against a variety of bacteria and other toxins (Fig. 2). It was postulated, then, that the corticoids would enable one to "buy time," i. e., to keep the patient alive until properly indicated antibiotics would have sufficient time to take effect, and/or would enable one to improve the status of such a patient to permit of early definitive surgery. It was felt that the proper use of broad-spectrum antibiotics would protect the patient against any tendency to dissemination of infection which

† References 6 and 7.

‡ References 8-11.

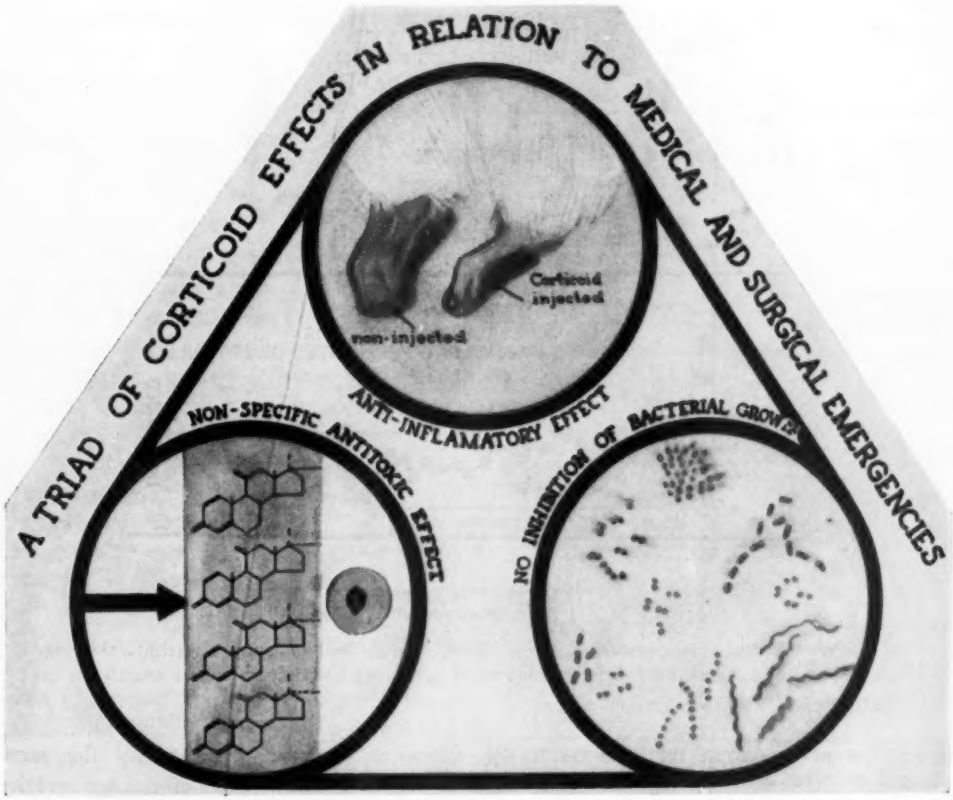
A TRIAD OF CORTICOID EFFECTS IN RELATION TO MEDICAL AND SURGICAL EMERGENCIES
Corticoid injected
non-injected
ANTI-INFLAMATORY EFFECT
NON-SPECIFIC ANTITOXIC EFFECT
NO INHIBITION OF BACTERIAL GROWTH

Fig. 2.—Corticoids (*a*) "build a wall" between toxins and cells (lower left); (*b*) inhibit inflammation (center) (rat paw preparation supplied by Hans Selye); (*c*) do not inhibit bacterial growth (lower right).

might result from inhibition of the inflammatory reaction by the corticoids. In this and affiliated institutions since that time, considerably more than 300 patients have been treated with such combined therapy. A portion of this experience is reported in detail in a recent paper.[13]

SPECIFIC CLINICAL CONSIDERATIONS

The first patient so treated was a child with generalized peritonitis, as the result of a ruptured appendix. From the history, the latter had occurred several days prior to the admission of the patient to the hospital. Despite antibiotic therapy, the child's condition was regarded as being extremely critical, and the decision was made to introduce corticoid therapy. In the space of 24 hours, the patient was almost free of fever, appeared clinically well, and not only had active peristalsis but had a spontaneous stool. The further course of this patient is described elsewhere.[14] Experience with him and with other similar patients indicated beyond any reasonable doubt that the combination of hormonal and antibiotic therapy not only might be lifesaving, but would permit of early surgery and rapid uncomplicated convalescence, if one adhered strictly to a proper program. Generalized peritonitis is, therefore, regarded as a specific indication for combined therapy. Also, combined therapy has been employed since 1950 in patients with meningitis of unusual severity and in patients with meningococcemia, with or without meningitis. As in the case of patients with peritonitis, initially such therapy was reserved for those who entered the hospital in a moribund or near-moribund state.

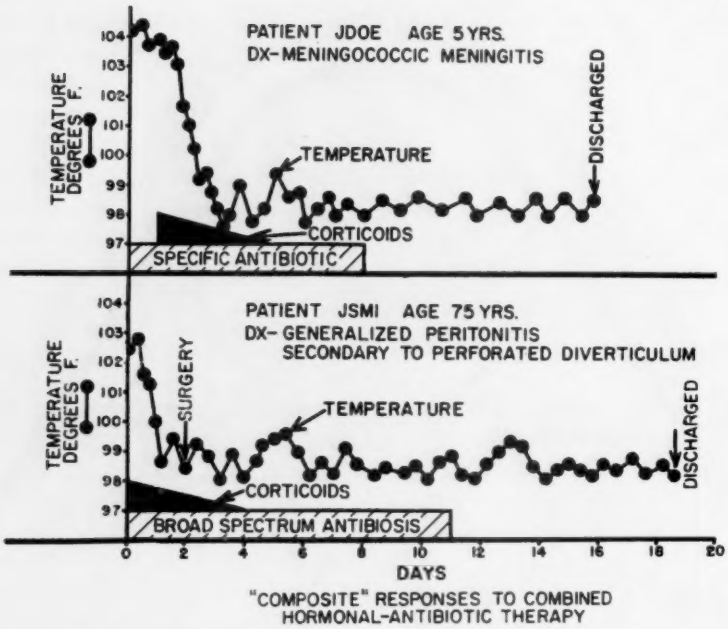

Fig. 3.—"Average" temperature curves in hypothetical medical and surgical patients, showing usual response and progress with combined therapy. Actual temperature curves are shown in other reports (see text).

As it became apparent that the results of combined therapy were salutory, and that untoward effects were conspicuously absent, the use of such therapy was extended to meningitis patients in a less severe category. At the present time, all patients with meningococcemia, with or without Meningococcus meningitis, routinely receive combined therapy, as well as those with other bacterial meningitides of more than usual severity, assuming that a bacteriologic diagnosis is available and that the organism is known to be responsive to specific antibiotics. In Figure 3 are shown "average" temperature response patterns in patients with medical and surgical emergencies who have received combined hormonal-antibiotic therapy. Specific temperature and clinical-response curves are reported elsewhere.[13]

OTHER INDICATIONS FOR COMBINED HORMONAL ANTIBIOTIC THERAPY

Any bacterial infection of unusual severity for which a specific antibiotic is available constitutes a potential indication for initial intensive corticoid therapy. By the same token, bacterial infections of average severity (at least for the present) should be treated with antibiotics alone (with the possible exception of infections involving the central nervous system).

Generally speaking, infections for which antibiotics are not available contraindicate the employment of corticoids. On the basis of the experience of others as well as ourselves, however, there appear to be two exceptions to this rule; namely, severe viral hepatitis and mumps orchitis. In the former condition, it has been well established that intensive corticoid therapy can be effective therapy for patients in hepatic coma and that its premature discontinuance may be associated with reappearance of coma and rapid progression of the hepatic damage.§ Prolonged corticoid therapy, in association with adequate formula feeding, may be necessary in this condition.

§ References 15-19.

Intensive corticoid therapy for patients with mumps orchitis appears to be consistently associated with rapid and complete disappearance of all inflammation in the gonads. If therapy is instituted sufficiently early, it is probable that there will be no residual damage to the testis. No untoward effects have been observed.

Shock from any cause, with the possible exception of that resulting from simple blood loss when blood replacement is immediately available, may be considered an indication for corticoid therapy. If the response to intravenous hydrocortisone does not occur promptly, arterenol (Nor-epinephrine) may be coadministered. The antishock effect of the corticoids appears to be more "fundamental" and sustained than that produced by arterenol. It seems probable that the former effect is via favorable modification of cell membrane permeability, the latter only via constriction of the peripheral vascular bed. It is our impression that prompt therapy in such patients may quite significantly lessen the occurrence of "lower nephron nephrosis."

Tuberculous meningitis, unresponsive to intensive antibiotic administration, may also be considered an indication for combined therapy.[20] Since the advent of isoniazid therapy, however, no adjuvant hormonal therapy has been required in our institution.

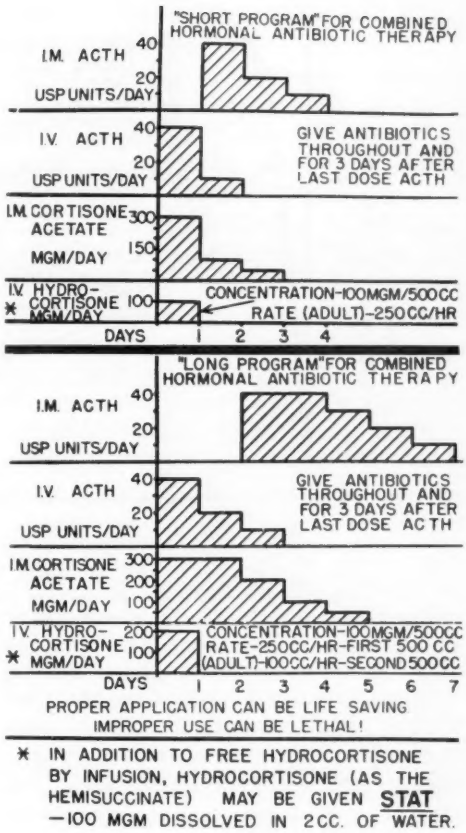

Fig. 4.—"Standard" emergency corticoid therapy. In a large majority of patients the "short-term program" is adequate.

SPECIFIC THERAPEUTIC PROCEDURES

In our institutions, for more than two years, one of two "standard" programs has been followed (Fig. 4). More than 80% of the patients who have been treated have received the short (four-day) program. Roughly 10% have been treated according to the seven-day program, and the remainder have been treated for longer (or occasionally shorter) periods of time.

The principles involved are as follows:

1. Very intensive initial therapy with both corticotropin and cortical steroids. During the past several months, we have had available hydrocortisone in propylene glycol and hydrocortisone hemisuccinate. With either of these, 100 mg. of hydrocortisone can be given intravenously in the space of a few minutes.‖ The blood levels obtained with the administration of 100 mg. of either of these materials are shown in Figure 5. On the basis of clinical response and eosinophile fall, it would appear that an effect can be demonstrated within less than 30 minutes after administration. The ability to administer a large dose

‖ The free hydrocortisone in propylene glycol was supplied through the courtesy of Dr. Edward Henderson, of the Schering Corporation; the hydrocortisone hemisuccinate was supplied by Dr. C. J. O'Donovan, of The Upjohn Company. One hundred milligrams of the former is contained in a volume of 4 cc.; 133.7 mg. of the latter is contained in one ampule vial (equivalent to 100 mg. of hydrocortisone). The addition of 2 cc. of sterile distilled water results in a solution which is chemically stable for several hours.

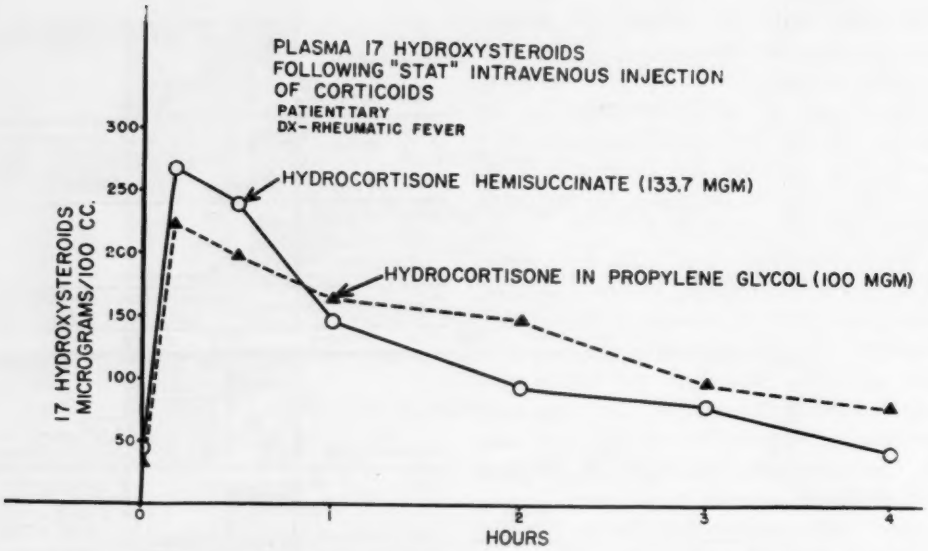

Fig. 5.—The amounts of hydrocortisone in the two preparations are identical. Metabolic effects are produced within 30 minutes and probably continue for some hours after the blood levels have fallen to normal. (From data of Michaels, G.; Friskey, R., and others: To be published.)

of cortical steroid in this fashion has been particularly valuable in the case of small children, to whom the previously available preparations (with a maximum solubility of 100 mg/500 cc. of aqueous solution) of necessity were administered slowly.

2. Gradual decrease in the amount of corticoids over the total period of administration.

3. Administration of corticotropin for one day longer than cortisone to eliminate any concern about residual adrenal atrophy!

4. Administration of antibiotics for at least three days after all corticoids have been discontinued. In the case of peritonitis, we now routinely administer antibiotic therapy for one week after the discontinuance of corticoids.

5. If combined therapy is to be used in patients with generalized peritonitis, or with any other emergency surgical condition, it is mandatory that the surgeon realize that definitive surgery must be carried out at the earliest moment that the patient can be considered a reasonably good operative risk. Only tragedy will result if any other course is pursued! It must be recalled that the corticoids so change the usual picture of disease that one's clinical judgment becomes worthless. Unless the surgeon is aware of this, he may be inclined to postpone surgery and thus to lose valuable time, as well as to run the risk of dissemination of infection. At the time of definitive surgery all free pus should be aspirated from the peritoneal cavity, followed by irrigation with saline and further aspiration, to minimize the likelihood of residual pockets of purulent material which later can result in abscess formation.

6. Initially, we had some concern regarding possible interference with wound healing in patients treated in this fashion. No difficulties of this sort have arisen in any patient whose nutrition prior to surgery was reasonably good. In malnourished persons corticoids must be administered for the shortest period of time compatible with survival.

7. It is essential that nutrition be maintained at an optimal level wherever possible, with particular reference to high-protein, high-potassium, adequate calorie, and low-sodium intake, because of the protein-catabolizing, potassium-losing, and sodium-re-

taining effects of the corticoids. Needless to say, in a surgical patient in whom gastric suction is being used, or in any patient in whom abnormal fluid loss is occurring, constant laboratory control must be observed to enable one to keep abreast of electrolyte and fluid requirements.

8. Anabolic steroids should be coadministered to all poorly nourished persons, or to those in whom corticoid administration is to be continued for more than four days. A single dose of 200 mg. of testosterone cyclopentylpropionate or nortesterionate (19-nortestosterone cyclopentylpropionate) may be adequate.

RELATIVE CONTRAINDICATIONS

In a patient who is critically ill, any contraindication to any therapeutic agent is relative. In general terms, corticoid therapy is contraindicated in patients with active tuberculosis, peptic ulcer, or major emotional instability. If, however, the condition for which the corticoid will be used is almost certain to be fatal unless corticoids are administered, the contraindication may properly be regarded as the lesser of two evils. In the tuberculous patient, one will administer intensive antibiosis for the tuberculosis, in conjunction with the corticoid; in the ulcer patient, an intensive antiulcer regimen will be instituted; and in the emotionally unstable patient, one will hope that a relatively short course of corticoid therapy will not precipitate a transient psychosis. On the basis of as yet limited observation, it seems probable that the employment of the new Δ^1 compounds (prednisone and prednisolone) will result in much lower incidence of mental and emotional disturbance.

In the patient with a poor myocardium corticoid administration, because of the sodium-retaining effect, is potentially hazardous. In this group also, the Δ^1 compounds may be superior.

THEORETICAL "HAZARDS"

As noted above, there are abundant animal data which indicate that under specific experimental conditions the administration of corticoids will increase the mortality of animals when they are exposed to infection. In all such experimental work, the corticoids have been employed in a totally different fashion than in the manner recommended for their clinical application.[21] It is well to emphasize again, however, that in infectious disease of whatever nature, inhibition of the inflammatory reaction breaks down the first line of defense against invading organisms. Hence corticoid therapy is to be used only in conjunction with potent antibiotics; further, one's objective is to use the minimal amount of corticoid therapy compatible with the desired therapeutic effect.

There are data from experimental animals which indicate that corticoids can inhibit the formation of specific immune proteins.¶ Again, the conditions under which such effects are obtained differ totally from those under which the corticoids are employed clinically (for emergency therapy). One might worry about such effects in patients on long-term intensive corticoid therapy, e. g., patients with the severe collagen diseases. Such patients, however, rarely manifest abnormal susceptibility to infection or inability to cope with spontaneously occurring infections.

Concern in regard to interference with wound healing has already been mentioned. As in the case of immune body formation, this appears to be a problem of no clinical importance, with the possible exception of extremely malnourished persons. In such patients corticoid therapy should be used only as a last resort.

There is one group of patients in whom corticoid therapy, emergency or otherwise, should be avoided, namely, those with widespread long-standing allergic dermatoses. The incidence of complications in these patients, in our experience as well as in the experience of others,[25] has been disturbingly high. Virulent metastatic infection may occur in such patients (usually staphylococcic, presumably as the result of migration of organisms from the skin into the general circulation, as the

¶ References 22-24.

result of inhibition of the inflammatory reaction). Perforated ulcer and mental aberration are also of common occurrence.

SUMMARY

On the basis of five years' experience with more than 300 patients having severe systemic infections, it appears that combined hormonal-antibiotic therapy, properly used, may result in lessened morbidity and mortality. Injudicious use of corticoids in such patients can produce precisely the opposite effect. The principles involved are as follows:

1. The vast majority of patients with infectious disease, as the result of the inflammatory reaction, the formation of specific immune bodies, endogenous adrenal cortex activity, and the proper use of antibiotics, make an uneventful recovery.

2. In a small group of patients, infection can result in fatality before the above agencies can be adequately mobilized. In such patients short-term, intensive corticoid therapy may result in rapid and profound diminution of systemic toxicity. Inhibition of the inflammatory reaction brought about by such therapy constitutes a potential hazard. This hazard can be adequately neutralized by the coadministration of properly indicated antibiotics and by discontinuance of corticoid therapy as rapidly as the patient's condition permits. It is essential that a precise program be followed.

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News and Comment

ANNOUNCEMENTS

New Publication.—Cardiovascular Disease: Data on Mortality, Prevalence and Control Activities, is a new publication of the Public Health Service, U. S. Department of Health, Education, and Welfare. Designed particularly for use by people working in the heart disease field, the booklet provides information on cardiovascular-renal disease mortality and prevalence and on heart disease control activities.

In general, data are included which permit comparisons among various population groups, among States, or among geographic regions. Results of casefinding where various populations were examined and various screening techniques used are also shown.

The 68-page booklet, issued as Public Health Service Publication 429, contains 36 tables. It was prepared by the Heart Disease Control Program of the Division of Special Health Services, Bureau of State Services, and single copies are available from the Heart Program.

Laboratory Refresher Courses.—The Public Health Service Venereal Disease Program has announced that nine laboratory refresher courses covering the serology of syphilis, management and control of syphilis serology by the regional laboratory, and tests for syphilis using Treponema pallidum will be offered at the Venereal Disease Research Laboratory in Chamblee, Ga., from September, 1955, through May, 1956.

The schedule of courses is as follows:

Sept. 26-Oct. 7, 1955	Serology of Syphilis
Oct. 24-Nov. 4, 1955	Serology of Syphilis
Oct. 31-Nov. 10, 1955	Tests for Syphilis Using the Treponema Pallidum
Jan. 9-20, 1956	Serology of Syphilis
Feb. 6-17, 1956	Serology of Syphilis
March 12-23, 1956	Serology of Syphilis
April 2-13, 1956	Serology of Syphilis
April 16-27, 1956	Tests for Syphilis Using the Treponema Pallidum
April 30-May 11, 1956	Management and Control of Syphilis Serology by the Regional Laboratory

The Serology of Syphilis courses are designed to provide refresher training to senior operating personnel of State and Public Health Service Laboratories. They include lecture, demonstration, and participation periods covering the most widely used American methods for the serodiagnosis of syphilis with references to latest developments in this field.

Courses about tests for syphilis using Treponema pallidum also include lectures, demonstrations, and some class participation in the immobilization (TPI), agglutination (TPA), complement-fixation (TPCF), immune-adherence (TPIA), and other tests using the virulent Treponema pallidum as an antigen source. The complexity of these tests requires that these classes be limited to small groups, but additional classes may be scheduled if there are large numbers of qualified applicants. Applicants for these courses should have had adequate experience in the field of serology and be in supervisory positions.

The course in management and control of syphilis serology by the regional laboratory, designed for assistant laboratory directors and senior laboratory staff members, includes review

of interlaboratory studies, laboratory inspection procedures, demonstration of antigen check-testing, control serum preparations, etc. This course will be expanded or repeated to accommodate overflow applicants.

Applications for any of the courses must be signed by the State Health Officer or State Laboratory Director unless the applicant is an employee of the Public Health Service. In such instances application must be approved by the Medical-Officer-in-Charge. Application blanks may be obtained from the address below. Reservations are made as soon as applications are received, and lists are closed one month before course starting dates. Correspondence about these courses should be addressed to Director, Venereal Disease Research Laboratory, Division of Special Health Services, PHS, Department of Health, Education, and Welfare, P. O. Box 185, Chamblee, Georgia.

Supplement to Immunization Information.—A supplement to the booklet "Immunization Information for International Travel" has just been released by the Public Health Service of the Department of Health, Education, and Welfare. It carries changes made in immunization requirements from June, 1954, to June, 1955. Persons having a 1954 edition of the booklet may obtain copies of the supplement, free of charge, from the U. S. Public Health Service, Division of Foreign Quarantine, Washington 25, D. C.

The booklet, including the new supplement, may be purchased for 20¢ from the Superintendent of Documents, Government Printing Office, Washington 25, D. C. A 25% discount is allowed on orders of 100 copies or more delivered to the same address.

The Academy of Psychosomatic Medicine.—The Academy of Psychosomatic Medicine will hold its Second Annual Meeting on Oct. 6, 7, and 8, 1955, at the Plaza Hotel, in New York. The subject of this year's scientific program is "The Psychosomatic Aspects of Drug Administration." There is no registration fee. Guests may attend the banquet.

Speakers include, among others, the following: Lester L. Coleman, M.D., who will talk on "Wonder Drugs—A Psychosocial Phenomenon"; Harry Kozol, M.D., discussing "Epilepsy: Modern Treatment with Drugs as a Keystone of Psychosomatic Method"; George B. Koelle, M.D., presenting "The Clinical Neuro-Pharmacology of Mescaline and *d*-Lysergic Acid"; Joseph E. F. Riseman, M.D., commenting on "Experiences with Placebos in the Treatment of Angina Pectoris"; Mark D. Altschule, M.D., presenting "Ideas About the Metabolism of Epinephrine," and M. Murray Peshkin, M.D., discussing the "Psychosomatic Aspects of Drugs in Allergy Practice."

A preliminary program can be obtained from the Secretary, Ethan Allan Brown, M.D., 75 Bay State Road, Boston. Reservations should be made directly with the Hotel, and a carbon copy should be sent to the Secretary's office.

Announcement of the Van Meter Prize Award.—The American Goiter Association again offers the Van Meter Prize Award of $300.00 and two honorable mentions for the best essays submitted concerning original work on problems related to the thyroid gland. The award will be made at the annual meeting of the Association, which will be held at the Drake Hotel, Chicago, May 3, 4, and 5, 1956, providing essays of sufficient merit are presented in competition.

The competing essays may cover either clinical or research investigations, should not exceed 3000 words in length, and must be presented in English. Duplicate typewritten copies, double-spaced, should be sent to the Secretary, Dr. John C. McClintock, 149½ Washington Ave., Albany, N. Y., not later than Jan. 1, 1956. The committee who will review the manuscripts is composed of men well-qualified to judge the merits of the competing essays.

A place will be reserved on the program of the annual meeting for the presentation of the winning essay by the author if it is possible for him to attend. The essay will be published in the annual proceedings of the Association.

Venereal Disease Postgraduate Course.—The 24th Venereal Disease Postgraduate Course for physicians sponsored by the University of Chicago and the Public Health Service will be given at the University of Chicago, Sept. 26 through Sept. 30, 1955.

The one-week course is designed to acquaint the practitioner with the latest developments in diagnosis, treatment, and management of the venereal diseases. No tuition will be charged for this course. Applications for admission are to be sent to the Section of Dermatology, Department of Medicine, University of Chicago, Chicago 37.

The faculty for this course will be drawn from various universities, the Public Health Service, and from outstanding authorities in the field. This course is accredited by the American Academy of General Practice.

Manual of Serologic Tests for Syphilis.—The Public Health Service of the U. S. Department of Health, Education, and Welfare recently announced release of the 1955 edition of the "Manual of Serologic Tests for Syphilis."

The Manual assembles the latest technical procedures to be observed in the performance of each of the reliable, evaluated serologic tests for syphilis now commonly employed in the United States. Included are the American Public Health Association, Hinton, Kahn, Kline, Kolmer, Mazzini, Rein-Bossak, and VDRL tests.

The new Manual (Public Health Service Publication No. 411) supersedes Supplements 9, 11, and 22 of the *Journal of Venereal Disease Information* and *VD-Graphic 85*. Copies may be obtained from the Superintendent of Documents, U. S. Government Printing Office, Washington, D. C. The price per single copy is $1.00.

Continuing Supply of Rhesus Monkeys for Medical Research and Production of Antipoliomyelitis Vaccine.—As result of negotiations, the United States Mission to India and the United States Embassy in India have secured the agreement of the Government of India to permit the continued exportation of rhesus monkeys for medical research and production of antipoliomyelitis vaccine. All needs must be certified by the United States Government through the Public Health Service.

Information concerning Public Health Service procedure and Certificate of Need forms may be secured from National Institutes of Health, Room 1012, Building T-6, Bethesda 14, Md. (Telephone number: Oliver 6-4000, Extension 2748, Miss Parent).

Cardiovascular Training Center.—Plans for the establishment of a pilot Cardiovascular Training Center for Nurses were announced today by Surgeon General Leonard A. Scheele, of the Public Health Service, U. S. Department of Health, Education, and Welfare. First of its kind, the Center will be located at the University of Minnesota School of Public Health, starting Jan. 1, 1956.

Cooperating with the Public Health Service in the project are the Minnesota Department of Health, the University of Minnesota School of Public Health, and other agencies in Minneapolis and St. Paul, which will offer trainees field experience in special services for cardiovascular patients.

Nurses for the first group to train at the Center will be drawn mainly from the consultant, supervisory, and instructor positions. Candidates to represent the various fields of nursing—hospital, industrial, nursing education, and public health—as well as different sections of the country will be accepted.

Dr. Gaylord Anderson, Director of the School of Public Health at the University of Minnesota, said, "This is not an attempt to prepare nurse-specialists but rather to give nursing leaders a better understanding of new developments in the cardiovascular field and of how to apply these developments to the nursing care of patients, both in the home and hospital." Dr. A. J. Chesley, Minnesota State Health Officer, commented that the Health Department welcomes the opportunity to cooperate in the Center which "we feel will offer unusually excellent experience for all trainees."

Miss Lola Hanson and Miss Margaret Denham, nurse consultants in the Service's Heart Disease Control Program, will serve as liaison between the Public Health Service and the Center. Miss Mildred Jones, also a Heart Program nurse consultant, has just left for Minneapolis to be Public Health Nurse Coordinator at the new Center.

Applications for the Training Center are being received at the University of Minnesota School of Public Health. Early applications are urged since the first group will be limited, with studies scheduled for one quarter.

CORRECTIONS

In the review of "Menstruation und innere Medizin," by Friedrich-Horst Schulz and H. Knobloch, in the July, 1955, issue of the A. M. A. ARCHIVES OF INTERNAL MEDICINE (p. 136) the name of the publisher was incorrectly given. This book is published by VEB Georg Thieme, Hainstrasse 17-19, Leipzig C 1, Germany.

In the article, "Newer Concepts of Experimental Obesity," by Mildred Fertman, M. A., M.D., in the June, 1955, issue of the ARCHIVES, an error occurred in the citation of the findings of Owen and co-workers. The fifth sentence of the second paragraph under "B. Traumatic Factors" should read: "Owen and co-workers found no significant weight loss in the control animals, as compared with variable weight losses in the gold-thioglucose-injected mice, when on a diet diluted 80% with kaolin."

Books

From this issue on, Dr. William Bean, of the ARCHIVES Editorial Board, will have charge of the BOOKS section. Dr. Bean brings to this task a keen interest in the cultural as well as the clinical aspects of medicine. Those familiar with his writings are aware of his background of solid scientific accomplishment, his compulsion to be fair and honest, and his unusual flair for the writing of pungent and elegant prose. His aim will be to give our readers a thoughtful appraisal of the new books that will be of interest to internists. The Editorial Board feels that its gratification over his willingness to accept this assignment will be shared by all of our readers.

PAUL S. RHOADS, Chief Editor

Colloquia on Ageing: Vol. 1. General Aspects. By the Ciba Foundation. Price, 30 s. Pp. 255, with 64 illustrations. J. & A. Churchill, Ltd., 104 Gloucester Place, Portman Sq., London, W. 1, 1955. (This book is published in America under the title Ageing: General Aspects, Vol. 1; price, $6.75; pp. 255, with 64 illustrations; Little, Brown & Company, 34 Beacon St., Boston 6, 1955.)

In our rapidly moving scientific age, the printing press, despite its frantic efforts, scarcely keeps up with recent changes. In trying to bring current material before the avid reading public, and perhaps for other reasons, the last ten years has seen a great increase in publication of books

WILLIAM B. BEAN, M.D.

reporting the proceedings of meetings. These have varied from the presentation of formal papers with little general discussion to an almost verbatim transcription of conversaziones, revealing both intellectual fire and emotional smoke. For the most part such books deal with the probing and advancing patrols of an army of scientists attacking the unknown. They also represent conferences of patrol leaders with general staff officers. Of the two books here considered, the "Colloquia on Ageing" consists of a series of papers, on the whole somewhat more mature and formal than those in the symposium on Cerebrovascular Diseases, perhaps because the topic encompasses broader and more comprehensive principles. Discussion frequently indicates the semantic complexities of defining so complex a process as ageing without prior definition of life or of time. It may be surprising to those not more conversant with the field to find out how

much actual work has been done along experimental and clinical lines to clear the way for a detailed attack on the problem. The main usefulness of this first of a series of colloquia on ageing is as a statement of the pioneering and exploring work. A vast unknown land has been looked at from new vantage points, even though from a distance. Having laid down definitions, marked out a few boundaries, and posed the problem, the next stage is to go back and collect more information, extend the maps, and analyze the significance of the findings. This, the first of the series of colloquia, emphasizes changes in human tissues with age, general pathologic findings, skeletal changes, metabolic changes, mental changes, nutritional factors, and many others. It reflects the present, somewhat tentative, research on ageing. Its approach is in harmony with the increasing tendency for an ecological view of sociomedical problems. It should appeal to those whose interests are academic, clinical, or general.

WILLIAM B. BEAN, M.D.

Cerebral Vascular Diseases. By Irving S. Wright, M.D., and E. Hugh Luckey, M.D. Price, $5.50. Pp. 167, with 5 illustrations. Grune & Stratton, Inc., 381 4th Ave., New York 16, 1955.

"Cerebral Vascular Diseases" is the transcript of a conference. Formal papers were not presented, but several monologues provided the theme for the individual sessions. The result is naturally very uneven, but it highlights well the known and unknown aspects of the diseases under consideration. The excitement and stimulus of such a conference is well reflected even though we may suppose there has been some expunging by the editor. In fact, sometimes it is a little embarrassing for the reader who feels that he has inadvertently stepped into the midst of a family quarrel. Unfortunately, this type of book is never as valuable for the reader as it is for those who participate in the conference which produces it. When one goes to the trouble of having a book made of such a conference, certain obvious omissions, oversights, errors, or even unaccountable lapses of information stand out glaringly to be recorded for posterity and the embarrassment of those caught napping. The book loses a good deal of value because the references are very inadequate. They appear in only certain sections of the report. The index is meager.

A few specific comments: Neurologists have not yet gotten away from their awkward redundancy of the expression "space occupying lesion" as though there could be lesions that did not occupy space; emboli is used in the singular, as are data and sequelae. There are a few remarkable statements such as "Does the chronology precede the electroencephalogram?", the word "level," which tends to get out of hand at conferences, makes one stop and think several times before meaning emerges from the statement that "anticoagulant levels were above the desired level." Also, it seems a pity that when some simple fact which has eluded the company is available it is not put in later by the editor as a footnote.

This book and the "Colloquia on Ageing" are both very stimulating and are excellent representatives of two different kinds of conference. How the authors will feel about their somewhat casual words and views, achieving the immortality of the printed page, when looked at in the cold afterthought of 10 or 20 years, is an interesting matter for reflection.

WILLIAM B. BEAN, M.D.

Surgery of the Alimentary Tract. By Richard T. Shackelford, M.D., assisted by Hammond J. Dugan, M.D. Price, $60.00, for the set of three volumes. Vol. 1, pp. 1 to 862; Vol. 2, pp. 863-1633; Vol. 3, pp. 1635-2575, with 1705 illustrations through Vols. 1, 2, and 3. W. B. Saunders Company, 218 W. Washington Sq., Philadelphia 5, 1955.

Thirty-one years have gone by since Bickham published his six-volume compendium on surgery, including general operations and the specialties. A revision has long been needed, and many years ago the publishers asked Dr. Callander to take on this task, which was started but not completed at the time of his death. Now Dr. Shackelford has wisely taken over only the gastrointestinal section and has rewritten it with completeness and great merit.

Of particular value is the fact that the three new volumes are not just descriptions of operations, as was the original Bickham, but that there is added some evaluation of the various procedures from the experience of Dr. Shackelford and reports from the literature, so that the reader is offered opinions aiding in making a decision on what to do. Thus for more reasons than operative technique will one want these books on hand. For each disease the surgical

anatomy and physiology of the organ is described, and there is a concise modern review of the etiology, symptoms, diagnosis, pathology, and principles of treatment. A subject is often covered much better than in most textbooks of surgery. Special points on what to avoid are emphasized, postoperative care is presented explicitly, and, finally, the results of the various operative procedures are listed from good references.

Shackelford's volumes are profusely and beautifully illustrated, with the originals from many sources. Not being redrawn, the pictures are not uniform, but the additional cost of the extra artist work would not be at all worthwhile when compared to the frequency with which illustrations have been put in to emphasize some small but important point. One gets an excellent visual picture of the treatment procedures and commonly a complete sequence of illustrations from some master surgeon is included to show his way of doing things. Being interested in gastrointestinal surgery, I recognize most of these illustrations. They are up-to-date and from the best sources.

It is not possible in this review to give credit to the great amount of material presented in these three volumes, but it is immensely comprehensive from esophagus through anus. All surgeons interested in gastrointestinal procedures will want to have these volumes available. They should be added to every hospital library for the interns and residents to read, since they are the very best of recent source material on this subject and will be valuable for a long time. For ready reference, the busy general surgeon will need them among his current books. While they are expensive, they are certainly legitimate professional tax deductions and are part of the great background of recorded surgical experiences from which we continually draw on in our efforts to be masters of our art.

WALTER G. MADDOCK, M.D.

Heart. By Aldo A. Luisada, M.D. Second edition. Price, $15.00. Pp. 680, with 312 illustrations. Williams and Wilkins Company, Mount Royal and Guilford Aves., Baltimore 2, 1954.

This is the second edition of a textbook of cardiology which serves as an excellent companion piece to the author's recent book, "The Heart Beat."

The author opens his preface to the first edition with the statement that the book "has been written for the large group of physicians who desire to increase their knowledge of heart disease." Such a statement might lead one to believe that this is just another textbook of cardiology. Further inspection reveals that this text is a new departure in approach to the subject of heart disease, one which has been lacking in textbooks for some time.

Recent thinking and teaching in the field of heart disease has stressed the "dynamic" approach —explaining abnormalities and disease in the light of physical principles of hemodynamics and normal function as revealed by more recent techniques of study. It is strange that more of the recent textbooks of cardiology have not followed this approach, and it is gratifying to see that Dr. Luisada has forsaken the more classical methods to write a textbook of cardiology which is based on applied physiology and physics.

In general, each condition is considered in an orderly way, the usual order being etiology, pathology, signs and symptoms, specific local signs and graphic phenomena, x-ray and electrocardiograms, course and complications, diagnosis, and treatment. Throughout, however, the significance of altered function is stressed and explained by means of numerous diagrams and graphic tracings.

The illustrations and diagrams are simple, clear, and well reproduced. The index is complete. Although it is not in the encyclopedia class, the book is very complete and well written. It is highly recommended for any internist, student, or cardiologist.

JACQUES M. SMITH, M.D.

Reserpine in the Treatment of Neuropsychiatric, Neurological, and Related Clinical Problems. Edited by Roy Waldo Miner. Price, not given. Pp. 280. The New York Academy of Sciences, 2 East 63rd St., New York 21, 1955.

"Reserpine in the Treatment of Neuropsychiatric, Neurological, and Related Clinical Problems" is the subject of the April 15, 1955, issue of the *Annals of the New York Academy of Sciences.* Thirty papers describe the neuropharmacology and clinical uses of the drug. Two of the papers report the use of chloropromazine as well as the use of reserpine. The papers were the result of a conference on reserpine held by the Section of Biology of the New York Academy of Sciences on Feb. 3 and 4, 1955. Included are reports on the use of reserpine in the various psychoses and neuroses, ambulatory and hospitalized geriatric psychotics, essential hypertension, chronic schizophrenic reactions, shock-reversible and shock-resistent patients,

chronically disturbed psychotic patients; irritable and hypertonic infants; office and private psychiatric practice; organic convulsive states, enuresis, and head injuries; epilepsy and behavior problems in children; narcotic withdrawal sickness; dermatological therapy; preoperative, peroperative, and postoperative sedation; headaches, and chronic bronchial asthma and chronic pulmonary emphysema.

The general tone of perhaps the majority of the reports is one of qualified optimism. Reserpine appears to be establishing for itself a definite place in the armamentarium of psychiatric treatment, although it now does not seem likely that it will completely replace any of the other presently accepted methods of psychiatric treatment. It appears to be of most value in "tranquilizing" agitated or disturbed psychiatric patients, without producing narcosis or hypnosis, and is of least value in the treatment of depressions. Dosage has to be individualized for the given patient. Of special interest is the observation made in a number of the papers that reserpine makes patients more accessible to psychotherapy. "We may be entering a New Era," states Sydney Kinnear Smith, "because of a better integration between the several schools that constitute our specialty. The Couch may yet be moved from the Ivory Tower to the Temple of Aesculapius."

A word of warning, however, should be sounded against the indiscriminate use of reserpine to treat psychiatric patients. The drug should not be used without a detailed knowledge of its effects and side-effects or without a thorough knowledge of psychopathology and psychodynamics. Some patients become temporarily more disturbed and others go into depression. Hoffman and Konchegul comment: "This drug demands that every other therapeutic resource available be used intelligently in the further treatment of our patients, for the patients who respond to reserpine are now more accessible to such therapy. Rather than solving the difficult problems of the hospital treatment of the mentally ill, the availability of a drug such as this introduces grave problems for while the burdens of caring for the disturbed are lessened by reserpine, the challenge of providing the appropriate additional psychiatric treatment for those no longer disturbed will tax all of our ingenuity, skill, and resources."

Unfortunately, none of the papers deals with the use of reserpine in the treatment of acute alcoholic agitations, although one report describes promising results in its use to prevent withdrawal sickness in narcotic addicts.

W. B. SPRIEGEL, M.D.

Advances in Internal Medicine: Vol. 6. Edited by William Dock, M.D., and I. Snapper, M.D. Price, $10.00. Pp. 375, with 103 illustrations. Year Book Publishers, Inc., 200 E. Illinois St., 1954.

This book consists of reviews of ten subjects, each with excellent and extensive bibliographies. Most of the topics are of general interest to internists, and all are timely and include the most recent facts and experimental data. The material is written in a coherent simple fashion, well interpreted and summarized.

One of the topics, diaphragmatic hernia, by Sidney Weintraub, reviews all aspects of this condition including the physiology, complications, and differential and x-ray diagnosis, with illustrations and treatment, both medical and surgical.

A. F. Willebrands and J. Groen give two methods of determination of insulin in blood and discuss the significance and uses of these tests including physiology and factors involved in their clinical applications. Their data are given showing blood insulin values in normals in man and values in diabetes mellitus, hyperinsulinism, islet-cell adenoma, insulin resistance, diabetic coma, etc. The normal value has been shown to be about 10^{-4} units of insulin per milliliter of blood.

A provocative discussion of uropepsin, by Donald C. Balfour Jr., indicates the potentialities of this relatively simple urine test in peptic ulcer, gastric carcinoma, and pernicious anemia. Diagnosis of emotogenic hyperacidity apropos of vagotomy in treatment versus gastric resection in treatment is an especially fascinating possibility. The effect of steroid therapy on gastric acid secretion may be followed by and somewhat regulated by studies of urinary uropepsin.

The theory and practical applications of special vectorcardiography are made very comprehendible in a section by Arthur Grishman. The "cube" and the "orthogonal" methods for symbolization are discussed. The teaching value of the spacial method is mentioned, as is the greater diagnostic value over the conventional electrocardiogram in certain conditions such as bundle branch block with infarction and certain obscure types of infarction.

The Papanicolaou technique and its use in diagnosis of exfoliated cells from many organ systems is included in a section by Ruth M. Graham.

The physiology and possible role in diabetes of glucogon, the anti-insulin hormone, is thoroughly explained by Piero P. Fos, of Chicago.

Malcolm M. Hargraves relates in detail the interesting L. E. cell phenomenon, including excellent photomicrographs, a discussion of artificial L. E. cell production, and the details of laboratory diagnosis of L. E.

A comprehensive review of the porphyrias, by C. H. Watson, is too complicated in certain sections for easy reading. However, a simple classification is suggested, and the latest attempts at therapy are discussed.

The subject of thrombotic thrombocytopenic purpura is very ably reviewed by Karl Singer. A table of differential diagnosis and a discussion of etiology, pathogenesis, and treatment is included.

These topics and bibliographies hold value for the person with research interests and are also clinically well oriented to the needs of the practitioner.

ROBERT S. NORMAN, M.D.

Should the Patient Know the Truth? Edited by Samuel Standard, M.D., and Helmuth Nathan, M.D. Price, $3.00. Pp. 159. Springer Publishing Company, Inc., 44 E. 23rd St., New York 10, 1955.

The very title of this series of questions on patient-physician relationships and matters of medical morality suggests that there is such a thing as "the truth," that this is known to the physician, and that it is sometimes kept away from the patient. In actual fact, as many of the interesting and different essays in this collection clearly set forth, the problem is much more complicated than that. To begin with, the problem concerns the truth merely when it is unpleasant. When the prognosis is good, the diagnosis indicates a benign course or benign lesion, or when nothing bad has been found, there is no question in anyone's mind. On the other hand when the disease is serious, when the outcome is in doubt, or when death is anticipated and, particularly, when some form of malignant tumor forms the basis of the patient's trouble, the questions are very perplexing. There is, in fact, no consensus on this matter, and I believe that all the just physician can state dogmatically is that what the patient is told should be true but not necessarily all that the physician knows should be told. Actually the problem and an effort to solve it have nowhere been stated better than in H. J. Henderson's essay on "The Physician and Patient as a Social System," in the *New England Journal of Medicine* **112**:819, 1935.

WILLIAM B. BEAN.

Viral Hepatitis: Clinical, Laboratory, and Public Health Aspects. By Heinz F. Eichenwald, M.D. Price, $0.55. Pp. 59, with 11 illustrations. United States Government Printing Office, Washington 25, D. C., 1955.

Viral hepatitis, a disease which, surprisingly, turned out to be the major epidemic of infectious disease in World War II, has received intensive study then and since that time, but, in spite of the tremendous amount of research, advances in our understanding of the disease have been disappointingly meager. This volume is particularly useful as a manual for health officers, army physicians, and those in practice away from large centers. It sets forth in detail methods for diagnosis, treatment, and, hopefully, for prevention. The manual was intended just for such purposes. Theoretical discussion is necessarily short. Also, the clinical side of the argument is not nearly so detailed or as well covered as the laboratory procedures. Altogether, this is a very useful and convenient field manual, which does not pretend to be anything else.

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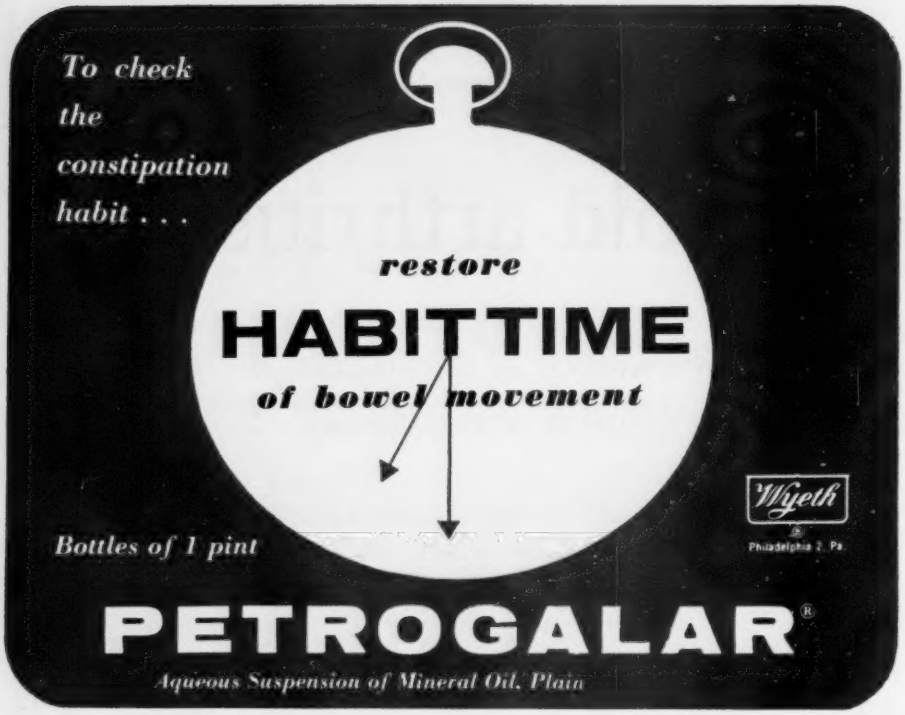

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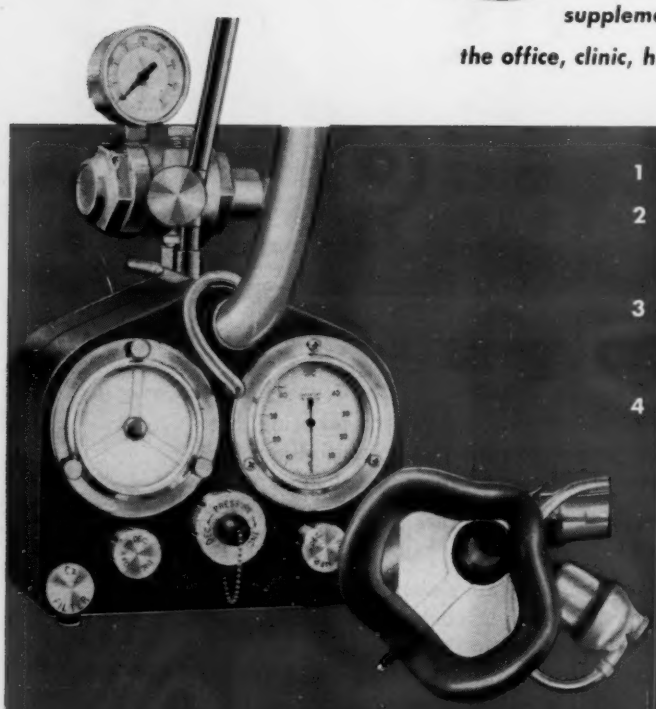

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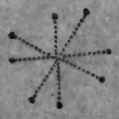

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